DE NOVO CLASSIFICATION REQUEST FOR SENSIMED TRIGGERFISH®

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Diurnal Pattern Recorder System.** A diurnal pattern recorder system is a non-implantable, prescription device incorporating a telemetric sensor to detect changes in ocular dimension for monitoring diurnal patterns of intraocular pressure (IOP) fluctuations.

NEW REGULATION NUMBER: 21 CFR 886.1925

CLASSIFICATION: Class II

PRODUCT CODE: PLZ

BACKGROUND

DEVICE NAME: SENSIMED Triggerfish®

SUBMISSION NUMBER: DEN140017

DATE OF *DE NOVO*: May 6, 2014

CONTACT:
SENSIMED AG
Route de Chavannes 37
1007 Lausanne
Switzerland

REQUESTER'S RECOMMENDED CLASSIFICATION: Class II

INDICATIONS FOR USE

The SENSIMED Triggerfish® is a prescription device indicated to detect the peak patterns of variation in intraocular pressure over a maximum period of 24 hours to identify the window of time to measure intraocular pressure by conventional clinical methods. The SENSIMED Triggerfish® is indicated for patients 22 years of age and older.

LIMITATIONS

SENSIMED Triggerfish® is a prescription device intended for use in the home and clinic settings. The clinical utility of SENSIMED Triggerfish® is limited to identifying the potential time period of the diurnal increases of intraocular pressure (IOP) in patients with glaucoma and those suspected of having glaucoma.

SENSIMED Triggerfish® is an adjunctive tool to tonometry. Diagnostic or treatment decisions taken by the healthcare professional shall only rely on traditional tools and methodologies.

Contraindications

- Active eye disease, eye injury or eye abnormality affecting the cornea, conjunctiva, or eyelids
- Patient history of eye or eyelid infections including sties or history of adverse events associated with wearing contact lenses, or intolerance, or abnormal ocular response to contact lenses
- Active inflammation of the eye
- Active infection of the eye
- Corneal vascularization
- Insufficiency of lachrymal secretion
- Corneal hypoesthesia
- Known allergy to silicone

Select Warnings and Precautions

- The sensor is intended for use on the surface of the eye. Do not implant the sensor.
- The sensor is not intended for wear beyond the 24-hour assessment period.
- The patient should not drive vehicles or handle dangerous machinery while wearing the sensor.
- The sensor is intended for single-patient, one-time use and should not be re-sterilized.

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

DEVICE DESCRIPTION

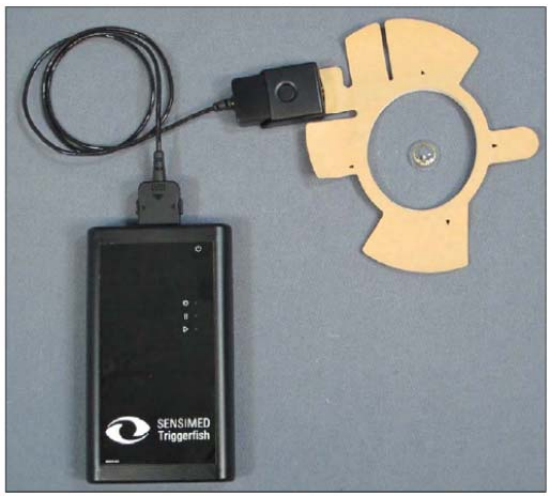


Figure 1: STF Diurnal Pattern Recorder System

SENSIMED Triggerfish® diurnal recording system (hereinafter **"STF")** is a small patient-worn electronic device intended for use in the home and clinic settings for recording diurnal patterns of IOP fluctuations (Figure 1).
The components of the STF are as follows:

- a hydrophilic, single-use soft contact lens with a strain gauge sensor
- antenna with a telemetry chip embedded within it, allowing for continuous wireless recording of changes in ocular dimension
- an external adhesive antenna worn around the eye is used to send power to, and receive measurement data from, the embedded system.
- a pocket-sized, battery-operated recorder worn by the patient during the 24-hour recording session, which is connected to the external adhesive antenna by a data cable.

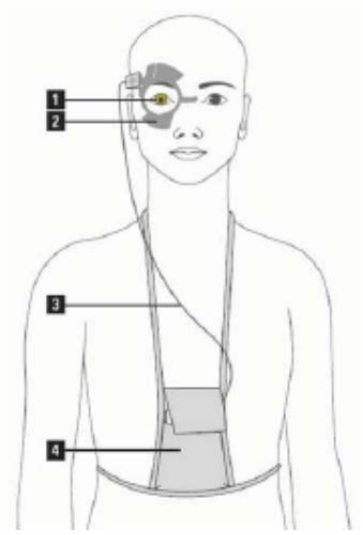


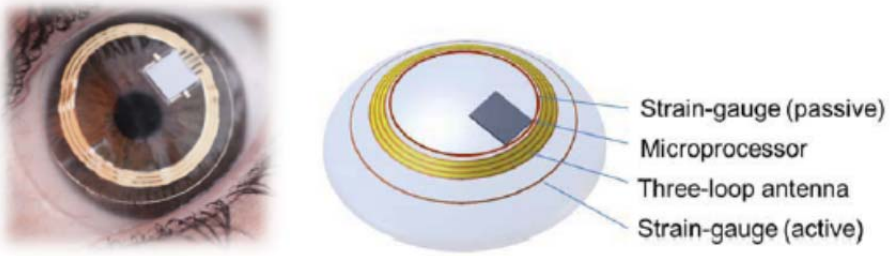
Figure 2: Main components of STF

A schematic of the components of the STF worn by the patient is shown in Figure 2 and includes:

1. Ocular Telemetry Sensor
2. Antenna
3. Data Cable
4. Recorder

Additional components: (charger to recharge the Recorder, Bluetooth universal serial bus (USB) adapter for communication between Recorder and doctor's personal computer (PC), and software for initiation recording sessions, and retrieval & display of the recorded data

In the Figure 3(*A-C)* below are more detailed images of the patient-wearable components:

The components of the sensor is shown in the following illustration: 	Figure 3 *A*: Ocular telemetry sensor (1)
	Figure 3, *B*: Right and Left Antenna (2)
	Figure 3,*C*: Portable recorder (4)

The operating principle of the STF is based on the measurement of circumferential changes of the eye ball at the corneoscleral interface by an active strain gauge embedded into the periphery of a soft silicone contact lens ("ocular telemetry sensor"). During the 24-hour recording session, the sensor wirelessly transfers the data to the recording system. At the end of the recording session, all data can be transferred to the PC for review and analysis by a healthcare professional.

SUMMARY OF NONCLINICAL/BENCH STUDIES

PERFORMANCE

The applicant provided two *ex vivo* porcine eye studies to validate the measurements of the device. The objective of the studies was to demonstrate the ability of the contact lens sensor to detect dimensional changes in relation to physiological-scaled changes in simulated pressure in enucleated (i.e., *ex vivo*) pig eyes.

The experimental setups of both studies used cannulated porcine eyes; for each eye, the STF contact lens was placed on the cornea and the cannula was connected to a manometric pressure sensor and a syringe which could effect changes in volume of the solution in the system.

The first study was performed to validate the relationship between the output of the wired contact lens strain gauge sensor and changes in ocular volume in an enucleated pig eye. The study demonstrated a strong correlation (r^2=0.992) between the sensor output and the control manometric pressure, supporting the conclusion that the contact lens sensor can detect changes in volume in an enucleated pig eye that corresponds to physiological IOP changes b (4) CCI/TS).

The second study was performed to substantiate the relationship between the output of the telemetric (wireless) contact lens sensor and changes in ocular volume in an enucleated pig eye. This study demonstrated the ability of the STF to detect dimensional changes in relation to physiological-scaled changes in IOP in an enucleated pig eye with both high sensitivity (i.e., ability to detect small simulated pressure pulsations) and high correlation (r^2 = 0.9935, simulated changes in IOP from b (4) CCI/TS).

SHELF LIFE/STERILITY

The contact lens with embedded telemetry sensor is packaged in b (4) CCI/TS) to ensure a Sterility Assurance Level (SAL) of 10 . The process was validated in a small steam sterilizer in accordance with ISO 11737-2:2009 "Sterilization of medical devices – Microbiological methods –Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process."

Shelf life testing was performed following real time storage at ambient conditions to establish a 24-month shelf life. The testing was conducted in accordance with ISO 11607-1:2006 "Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems, and packaging Systems" and ISO 11737-2:2009.

BIOCOMPATIBILITY/MATERIALS

The ocular telemetry sensor is fully embedded in a silicone elastomer, which is widely used in a variety of medical devices. The company provided sufficient evidence that the patient-contacting materials (i.e., silicone elastomer) of the device are biocompatible.

Specifically, the biocompatibility assessment of the silicone elastomer was conducted per ISO 10993-1:2009 "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing within A Risk Management Process" for mucosal membrane contacting devices with limited contact duration. In addition, the company conducted cytotoxicity (as per ISO 10993-5:2009), irritation, and sensitization tests (ISO 10993-10:2010) to demonstrate that the silicone elastomer is biocompatible. The applicant also conducted chemical analysis of leachables and extractables for the STF final finished ocular telemetry sensor. The extracts were analyzed quantitatively and qualitatively by b (4) CCI/TS The amount of organic substances in the extracts was below the limit of quantification b (4)).

The antenna is composed of medical grade foam b (4) CCI/TS) and hypoallergenic adhesive tape b (4) CCI/TS The foam and the adhesive are not in contact with the eye, only with surrounding skin. The biocompatibility information for the antenna and medical grade adhesive was based on the long history of safe use of these materials for medical devices and cytotoxicity testing conducted per ISO 10993-5:2009. Based on the well-established biocompatibility and common use of these materials, further biocompatibility testing is not necessary.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

Verification testing was performed according to IEC 60601-1-2:2007 "Medical electrical equipment Part 1: General requirements for basic safety and essential performance," including compliance with US National differences. Electromagnetic compatibility of the device was supported by demonstrating compliance with the Electromagnetic Compatibility standard IEC 60601-1-2:2014 tested for the home healthcare environment. This included an evaluation of potential interference to and by the STF device from Bluetooth communication.

MAGNETIC RESONANCE (MR) COMPATIBILITY

The STF device is labeled as "MR Unsafe."

SOFTWARE

The software is considered to be a minor level-of-concern. This software is intended to accomplish the four high-level functions described below:

- Enable the user to configure the STF recorder device for a measurement session
- Control the functional operations of the STF device
- Retrieve measurement data from the recorder device and save the data in an encrypted format on a PC
- Enable the user to visualize the measurement data using chart plots; enable the user to edit some information in the data and add metadata information to the data

To accomplish the above functions, the sensor contains an embedded microprocessor, the recorder contains firmware, and the desktop computer contains software to operate the Bluetooth service, software to interact with the recorder, and software to display/store data.

The application included the following software-related documents, which are sufficient:

- Software Description
- Device Hazard Analysis
- Software Requirements Specifications
- Architecture Design Chart
- Design Specifications
- Traceability Analysis/Matrix
- Verification and Validation testing
- Revision Level History

SUMMARY OF CLINICAL INFORMATION

The primary data are provided by two US studies:

1. **Study TF-1005 – Glaucoma Suspects and Patients with Primary Open Angle Glaucoma (POAG)**

   Study Design: The study was a single-center, prospective, open label study in which STF recordings were conducted for 24 hours on the same eye of glaucoma suspects and subjects with POAG during two consecutive sessions 6-9 days apart. Upon completion of each recording session, an ophthalmic examination was conducted and subjects were asked to score their subjective comfort level using visual analogue scale (VAS) scale. The study aimed to accrue 20 eligible subjects of each of the two aforementioned populations, equating to a total of 40 subjects.

   Objective: The objective of the study was to assess the safety and tolerability of the STF Sensor wear during a 24-hour period in glaucoma suspects and subjects with glaucoma.

   Endpoints: Safety endpoints included adverse events, those that were device-related, and categorized by severity, resolution, and whether concomitant medications were employed. The primary endpoint for tolerability was the assessment of ocular discomfort using VAS (0 mm -no discomfort) to 100 mm -very severe discomfort) immediately after the end of the 24-hour sensor wear period. The primary endpoint was measured twice for each subject, once after each of 2 sessions. The secondary performance endpoints included best corrected visual acuity (BCVA), pachymetery, corneal staining, and ocular hyperemia.

   Data Analysis: For each subject VAS was used to assess comfort.

RESULTS:
A total of 41 subjects (25 male and 16 female, mean age 54.6 ±16.5 years) were enrolled in the study over an 8-month time frame. Out of the 41 subjects enrolled, 22 were glaucoma suspects and 19 were subjects diagnosed with glaucoma.

One subject in the glaucoma suspect group did not complete the study due to improper device fitting on the day of the first monitoring session and therefore, was excluded from the primary and secondary performance analysis sets. Thus, 40 subjects completed the study. One subject in the glaucoma group removed the sensor during the first session, but wore the sensor for the full 24-hour period on the second session. Both sessions were included in the analysis for safety, but the first session was excluded from the performance analysis. This occurrence does not affect the validity of the results as the study was designed to assess the safety and tolerability of the device rather than the effectiveness.

The mean duration of STF wear was 24.0 ±0.5 hours in the first session and 24.0±0.3 in the second session, hence equating to 80 24-hour exposures to STF.

Six device-related slit lamp findings of moderate or severe intensity occurred in a total of 79 evaluable eyes in 4 subjects (enrolled). Ocular hyperemia (severe) was the most common slit lamp finding, occurring in 4 (5.1%, 4/79) study eyes. No symptoms, problems and complaints were reported for subjects undergoing a second 24-hour ocular dimension recording session a week after the initial session.

Of all reported moderate and severe slit lamp findings, 100% resolved with no clinical sequelae. The mean time to resolution was 24.5±11.8 hours post utilization of the STF. There were no serious or unanticipated serious adverse device events reported in this study.

Comparison of the VAS score by group over the 2 sessions yielded no significant difference (p=0.336). No significant correlations were found between VAS and presence of ocular hyperemia, gender, or use of topical IOP-lowering medication.

Mean change from baseline pachymetry was not significantly different in both sessions, for each of the groups and for both groups combined. None of the subjects with abnormal corneal staining values showed corneal erosion.

Furthermore, Study TF-1005 demonstrated repeatability of the mean 24-hour STF profiles in 31 glaucoma and glaucoma suspect subjects, with a strong intraclass correlation (ICC) (0.99) between the mean profiles from two different sessions one week apart among all subjects.

2. Study TF-1009 – Healthy Subjects and Patients with POAG

Study Design: The study was a single-center, prospective, open label study in which the IOP pattern was recorded for 24 hours using the STF in healthy subjects and subjects with

POAG. The study was conducted at a sleep laboratory facility. The study aimed to accrue 30 eligible subjects.

Objectives: The objectives of this study were to assess the safety and performance of STF in recording of ocular dimensional profiles. The safety endpoints include all adverse events (AEs), including serious adverse events (SAEs). The primary performance endpoints include: 1) an ability of STF to detect wake-to-sleep (W/S) slope from one hour preceding the time of dark period initiation (going to bed) to one hour after, and 2) percentage difference between frequency of ocular pulsation as recorded by STF and the heart rate (HR) as determined by pulse frequency assessment scored dichotomously at each pair of parallel measurements. [1]

The secondary performance endpoints included subject's tolerability (acceptance) of STF, which was measured by questionnaire and presented descriptively on a 5-point analog scale where 5 indicates high acceptance of STF and 1 indicates low acceptance.

Subjects: Thirty (30) eyes of 30 subjects showing at least 3 mmHg difference between wake and sleep IOP were to be enrolled in the investigation. Should some subjects exhibit less than 3 mmHg difference between wake and sleep IOP, additional subjects were enrolled until 30 valid subjects were available. Healthy subjects (including subjects with ocular hypertension) and POAG subjects (including subjects with normal tension glaucoma) were eligible for the study.

Methods: Study subjects remained in a sleep laboratory environment throughout the 24-hour STF recording session. All participating subjects received a comprehensive ophthalmic examination before and after STF recordings. Pneumatonometry measurements were taken every 2 hours in the non-STF eye throughout the sleep laboratory housing. HR measurements were collected in the sleep period. Safety was evaluated through the collection of AEs, including serious adverse events (SAEs).

Results: Thirty-three subjects were enrolled in the study. In accordance with the protocol, 4 subjects (out of 33 subjects) were excluded from the primary analysis dataset. The exclusions were made for the following reasons: less than 80% of valid STF measurements were obtained within one hour before/after dark period (n=2), change of IOP from wake/sitting to sleep/supine as measured by tonometry between was less than 3 mmHg (n=1) and invalid STF recording (n=1). The data from all 33 subjects were included for the safety analysis dataset, while data from 29 subjects were included in the primary analysis set for performance.

[1] The STF device is not for the detection of the ocular pulse. The comparison of STF output to HR was done to demonstrate the ability of STF to capture small and fast changes by recording a physiologic phenomenon.

Safety:
Per eye analysis of Study TF-1009 reveals that there were a total of 11 device-related slit lamp findings. Seven (7) eyes of 33 (21.2%) displayed moderate corneal staining; and 1 eye (3.0%) and 3 eyes (9.1%) displayed moderate to severe injection (ocular hyperemia), respectively. However, no serious adverse events were reported.

Primary Performance

1. A positive slope was detected on STF profiles in the transition period from wake to sleep (W/S slope) in the study population.

2. The ocular pulse frequency (OPF) was stated to be within 15% of HR measurements in at least 70% of evaluable cases. In addition, the lower margin of the estimated confidence interval (CI) for accuracy of STF to detect the OPF was stated to be 75%, when using evaluable cases. However, due to large statistical measurement errors, the results are inconclusive.

   Although the study results are inconclusive for quantitative characterization of ocular pulsation profiles or W/S slopes, the results show the ability of the device to qualitatively capture (i) small and fast, and (ii) larger and slower patterns. The existence of predictable STF patterns supports the utility of the device as a tool for monitoring diurnal patterns of the IOP change as related to ocular dimensional changes.

Secondary Performance
The average subject tolerability was 3.7 on a 5 point scale (5 high acceptance; 1 low acceptance).

In a subsequent analysis of the TH-1009 dataset, a strong correlation ($r=0.956$, $p<0.001$, Pearson correlation) was observed between the mean 24-hour STF curve from one eye of 30 healthy subjects, to the mean 24-hour IOP curve collected from the fellow eye of the same 30 subjects. These results, based on dimensional changes of the eye, further support the link between the pattern of the STF output and 24-hour profile of IOP changes as measured by repeat tonometry.

Figure 4 below illustrates two STF profiles in which peaks and troughs occur at different times during the 24-hour period. In the eye with the dark blue STF profile, the peak occurs in the early morning and further assessment of the peak would therefore be advised at this time. In the eye with the yellow STF profile, the peak is recorded in the evening so further assessment of the peak would be advised at this time.

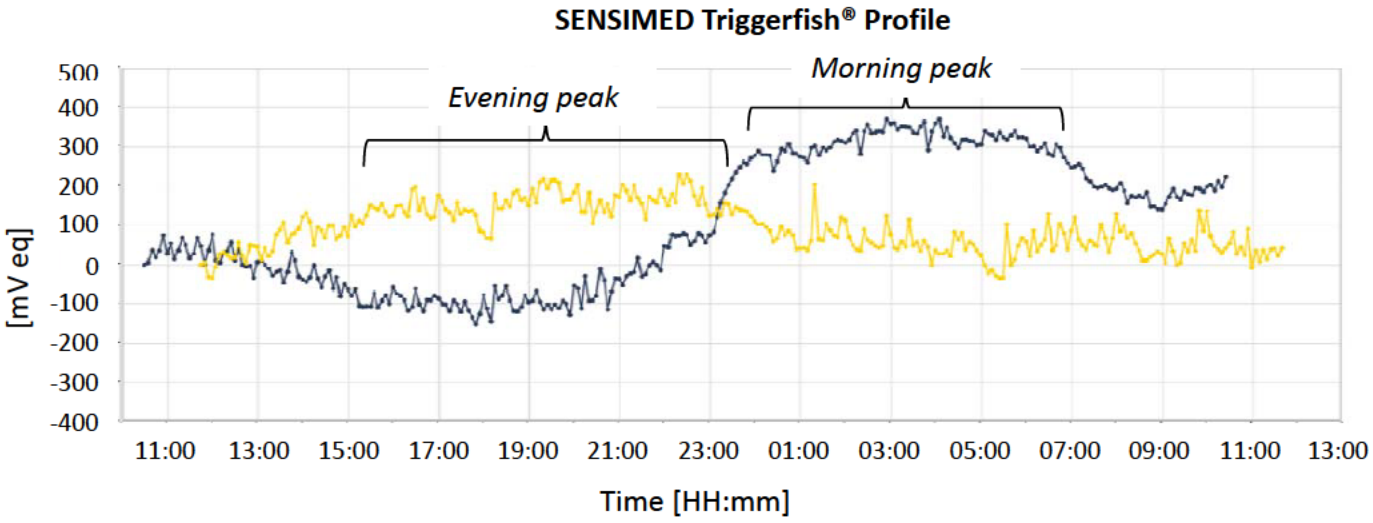


Figure 4: An example of STF Profiles

LABELING

The labeling satisfies the requirements of 21 CFR 801.109. The patient labeling also follows the principles identified in FDA's guidance titled "Medical Device Patient Labeling" (issued April 2001).

The company provided a user manual intended for the healthcare practitioner and patient labeling ("patient booklet").

The user manual includes a complete list of contraindications, warnings and precautions, and possible complications based on study experience. It also includes: a description of all major components and accessories; the principle of operation; all user-accessible controls and indicators; operating and maintenance instructions; and a listing of all moderate and severe grade adverse events (AEs) that have been observed in the US studies. The patient labeling includes all relevant contraindications, warnings, and precautions as well as a list of observed and probable complications. In addition, the labeling includes directions and considerations for the patient during the recording session regarding activities and things to avoid. Lastly, the patient labeling includes a description of the device and its indications for use, as well as how the data collection is used by the healthcare provider.

RISKS TO HEALTH

Table 1 identifies the risks to health that may be associated with use of the diurnal pattern recorder system and the measures necessary to mitigate these risks.

Table 1 – Identified Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measure
Ocular Adverse Events • Hyperemia • Punctate keratitis • Discomfort • Dry eye – dry sensation in the eye where the sensor is placed • Foreign body sensation – gritty feeling • Itching, burning • Swelling of eyelids • Pink eye • Excessive watering, unusual secretions or redness of the eye • Eye pain or irritation • Eye injury	Clinical Testing Biocompatibility Evaluation Labeling
Infection	Sterilization Validation Labeling
Adverse Tissue Reaction	Biocompatibility Evaluation Labeling
Software Malfunction	Software Verification, Validation, and Hazard Analysis
Hardware Malfunction	Non-clinical Testing
Use Error (e.g., improper fit, device manipulation)	Clinical Testing Labeling
Electromagnetic Interference with Other Devices	Electromagnetic Compatibility (EMC) and Electromagnetic Interference (EMI) Testing Labeling
Electrical Malfunction (e.g., shock, battery-related issues)	Electrical Safety Testing Labeling
Measurement Noise or Artifact Leading to Incorrect Graphical Representation of Variation	Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the diurnal pattern recorder system is subject to the following special controls:

1. Clinical performance data must demonstrate that the device and all if its components perform as intended under anticipated conditions of use. The following performance characteristics must be demonstrated:
    a. ability of the device to detect diurnal changes

b. tolerability of the system at the corneoscleral interface in the intended use population.

2. Non-clinical testing must validate measurements in an appropriate non-clinical testing model to ensure ability to detect changes in intraocular pressure.

3. Patient-contacting components must be demonstrated to be biocompatible.

4. Any component that is intended to contact the eye must be demonstrated to be sterile throughout its intended shelf life.

5. Software verification, validation and hazard analysis must be performed.

6. Performance testing must demonstrate the electromagnetic compatibility and electromagnetic interference of the device.

7. Performance testing must demonstrate electrical safety of the device.

8. Labeling must include the following:
    - Warning against activities and environments that may put the user at greater risk.
    - Specific instructions for the safe use of the device, which includes:
        - Description of all device components and instructions for assembling the device;
        - Explanations of all available programs and instructions for their use;
        - Instructions and explanation of all user-interface components;
        - Instructions on all safety features of the device; and
        - Instructions for properly maintaining the device.
    - A summary of non-clinical testing information to describe EMC safety considerations.
    - A summary of safety information obtained from clinical testing.
    - Patient labeling to convey information regarding appropriate use of device.

BENEFIT/RISK DETERMINATION

The patterns of diurnal changes of IOP are the result of an underlying physiological mechanism of aqueous humor production and outflow in addition to the biomechanical properties of the eye walls. Variations in aqueous production and outflow will impact both IOP and ocular dimension. As a manifestation of the same underlying physiological mechanism, changes in IOP and ocular dimensions will parallel each other, revealing patient-specific patterns and characteristics such as peaks or troughs over a 24-hour period.

The value of extending IOP measurements over a 24-hour period has been demonstrated where peak IOP was observed outside regular office hours. Such peaks may be an additional risk factor for the progression of glaucoma. Furthermore, even with attempts at serial tonometry, the exact timing of IOP peaks and troughs in a 24-hour cycle may be missed.

Currently available tonometers, including the gold standard Goldmann applanation tonometer, are unable to reliably identify the peaks and troughs in IOP, which each individual experiences over a 24-hour period of time. This is due to the fact that tonometry cannot be performed throughout the 24-hour cycle without disturbing sleep and, during waking hours, due to the limitations in the frequency at which tonometry can practically and safely be repeated.

The STF is a tool able to continuously record time-related patterns of ocular dimensional changes, thereby identifying the time window at which the intraocular pressure should be measured by a healthcare professional to aid in the management of glaucoma.

The major benefit of the STF device is that it allows the continuous monitoring of diurnal fluctuations in IOP by detecting patterns of dimensional changes at corneoscleral interface of the eye. The clinical studies conducted by the applicant showed a strong relationship between these patterns of ocular dimensional changes and diurnal fluctuation of the IOP. In addition, the 24-hour recording with the STF device can be performed not only in a clinical setting but also when the patient is involved in his/her normal daily activities in the home setting. Not only does this allow continuous monitoring of diurnal IOP fluctuations, but it also enhances the convenience to the patient and the eye care professional.

The risks of the device are based on data collected in the clinical studies described above. The most common moderate/severe non-serious events were ocular hyperemia (redness of the eyes), punctate keratitis (irritation of the corneal epithelium). These were all due to the contact lens portion of the device. Other procedure-related complications that a patient may be subject to, but were not directly observed in the clinical studies described above, are related to application of the contact lens sensor of the device such as corneal abrasion, keratitis and conjunctivitis. The mean time to resolution of the events was 66 hours. Per eye analysis of Study TF-1005 reveals that 7 device-related slit lamp findings and Symptoms/Problems/Complaints were reported for 6 out of 79 exposed eyes (7.6%) in two exposures. One eye had moderate corneal staining (punctate keratitis), 4 eyes had severe injection (ocular hyperemia) and one eye of one subject had a complaint of moderately blurred vision. Per eye analysis of Study TF-1009 reveals that there were a total of 11 device- related slit lamp findings. Seven (7) eyes of 33 (21.2%) displayed moderate corneal staining; and 1 eye (3.0%) and 3 eyes (9.1%) displayed moderate to severe injection (ocular hyperemia), respectively. However, no serious adverse events were reported.

In conclusion, given the available information above, the data support use of the STF for identifying the window of time at which the corneoscleral interface changes over a 24 hour period in response to volumetric changes in the eye, and the probable benefits outweigh the probable risks. The clinical studies conducted by the applicant demonstrated the relationship between these patterns of ocular dimensional changes and diurnal fluctuation of the IOP. The device provides substantial benefits and the risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The *de novo* request for the SENSIMED Triggerfish® is granted and the device is classified under the following:

Product Code: PLZ
Device Type: Diurnal Pattern Recorder System
Class: II
Regulation: 21 CFR 886.1925