DE NOVO CLASSIFICATION REQUEST FOR PEDIATRIC VISION SCANNER

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Strabismus Detection Device**. A strabismus detection device is a prescription device designed to simultaneously illuminate both eyes with polarized light for automated detection of strabismus by analyzing foveal birefringence properties.

NEW REGULATION NUMBER: 21 CFR 886.1342

CLASSIFICATION: CLASS II

PRODUCT CODE: PMW

BACKGROUND

DEVICE NAME: PEDIATRIC VISION SCANNER

SUBMISSION NUMBER: DEN130051

DATE OF DE NOVO: DECEMBER 13, 2013

CONTACT: REBISCAN, INC.
30 MOUNT AUBURN STREET, SUITE B
CAMBRIDGE, MA 02138

REQUESTER'S RECOMMENDED CLASSIFICATION: CLASS II

INDICATIONS FOR USE

The Pediatric Vision Scanner is intended for the automated detection of misalignment of the visual axes using polarized light. It is indicated for the screening of amblyopia and microstrabismus associated with amblyopia in children age 2 to 8 undergoing evaluation in a professional eye care setting and who are responsive to taking direction and who can pay attention for at least 5 seconds.

LIMITATIONS

Prescription Use only: Federal (USA) law restricts this device to sale by or on the order of a physician.

Warnings

1. Pediatric Vision Scanner (PVS) testing is not a substitute for a comprehensive eye examination. A comprehensive clinical examination is needed to confirm the results of the PVS.

2. The PVS is not a substitute for screening eye examinations in patients with systemic diseases with known ocular manifestations, such as juvenile idiopathic arthritis and neurofibromatosis. It is recommended that these patients undergo eye examinations per professional care guidelines.

3. Children with obvious ocular abnormalities (such as grossly visible strabismus, corneal scarring, cataract, ptosis (drooping eyelid)) should be referred regardless of the PVS result.

4. Children with developmental delays may not be sufficiently cooperative to follow directions and focus on the fixation target for short time periods during testing. In the pivotal clinical trial, children with developmental delays were excluded. It is unknown whether PVS testing will give accurate results in this population.

5. In the pivotal clinical trial, children with acute ocular problems were excluded. The accuracy of PVS testing on children with acute ocular problems (such as eye trauma, conjunctivitis, blepharitis, chalazion, and nasolacrimal duct obstruction) is unknown. PVS testing on such patients may lead to inaccurate results. It is recommended that you delay PVS testing in such patients until the acute condition has resolved.

6. Initial clinical trials of the PVS were conducted in a professional eye care setting. Results may differ if the device is used outside of the professional eye care environment.

7. The PVS does not identify risk factors for amblyopia or strabismus. It is designed to detect amblyopia and/or strabismus if or when these conditions are present or develop. (For reference, the American Association for Pediatric Ophthalmology and Strabismus considers the following refractive error thresholds as age-dependent risk factors for amblyopia: In children aged 12-30 months, astigmatism >2.0 D, hyperopia >4.5 D, and anisometropia >2.5 D; in children aged 31-48 months, astigmatism >2.0 D, hyperopia >4.0 D, and anisometropia >2.0 D; and in children >49 months of age, astigmatism >1.5 D, anisometropia >1.5 D, and hyperopia >3.5 D. (Donahue et al. *J AAPOS* 2013;17:4-8.))

Precautions

8. Patients with **intermittent strabismus** may be able to pass the PVS test if their strabismus is not present during testing at the standard testing distance. Referral should be based on clinical judgment rather than the results of the PVS.

9. Some patients with **incomitant strabismus** (variable angle depending on gaze direction) may turn or tilt the head in order to maintain good binocular alignment. Referral should be based on clinical judgment rather than the results of the PVS.

10. There are no optical safety concerns when PVS testing is performed on a patient wearing corrective lenses. However, doing so may lead to inaccurate PVS results, and removal of corrective lenses is recommended if PVS testing is to be performed. Children wearing corrective lenses who are already under the care of an eye care specialist should be advised to remain in compliance with their specialist's care and follow-up plan.

11. Please note that the PVS cannot quantify the degree of misalignment or degree of visual acuity reduction, and it does not diagnose specific disease conditions.

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

DEVICE DESCRIPTION

The Pediatric Vision Scanner (PVS) is a non-invasive, optical instrument intended to be used for ophthalmic diagnostic purposes. The device integrates all hardware components within the plastic enclosure, including the image acquisition optics, the system computer, and visual display.

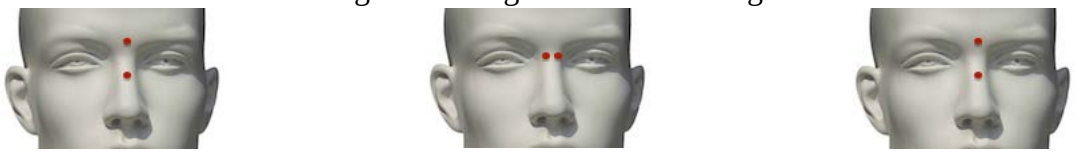
Figure 1: The Pediatric Vision Scanner Device

The PVS is to be held with both hands and level to the ground, with the aperture aimed toward the child. The operator positions the PVS in dim light as shown in Figure 2.

Figure 2: Positioning of the Device

Prior to each measurement, a background measurement is obtained to minimize signal interference. Rangefinders (laser diode, 650 nm wavelength) allow the proper positioning of the device (~ 0.5 meters) during background measurement and measurement as shown in Figure 3.

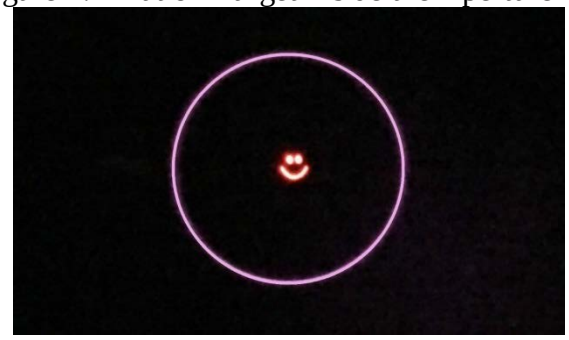
Figure 3: Rangefinder Positioning



A (too close) **B** (correct distance) **C** (too far)

After the background is obtained, the operator instructs the patient to open their eyes, peer into the lens (with both eyes), and fixate on a target light (red Light-Emitting Diode (LED)) source (in the shape of a "smiley face"; Figure 4).

Figure 4: Fixation Target Inside the Aperture



The operator performs the measurement; a spot of near-infrared (laser diode, 830 nm wavelength), polarized light rotates circularly around the fixation target.

Based on the polarization characteristics of the received light, the device uses an algorithm to determine whether or not this light is incident on the nerve fibers emanating from the fovea, the central retinal area for normal visual fixation, of each eye. Because the system uses relative measurements of fixation to diagnose amblyopia, it cannot detect forms of amblyopia which also

have fixation (e.g., amblyopia without strabismus). By this design, it is also unable to detect amblyopia independently in a single eye.

Based upon this analysis and determination, the following output information is presented to the operator:

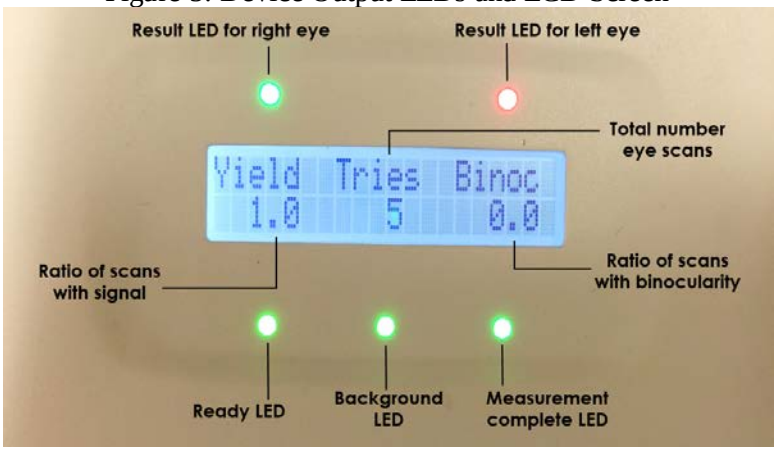
- LED outputs (based on binocularity values; Table 1)

Table 1: Dichotomous LED Results and Corresponding Outputs

Right LED	Left LED	Output
Green	Green	Pass
Red	Green	Refer
Green	Red	Refer
Red (flashing)	Red (flashing)	Refer bilateral

- "Tries": total number of scans (performed in two sets of 5, a maximum of 10)
- "Yield": ratio of number of scans that produced a signal to number of tries
- "Binoc" / "binocularity": the ratio of scans resulting in bilateral, simultaneous fixation to number of tries

Figure 5: Device Output LEDs and LCD Screen



The device has an optical portion and integrated software analysis to administer, interpret, and convey the results of a scan.

The optical portion of the device may be divided into two major pathways:

Illumination pathway: A beam of low-power, diverging, polarized laser light is directed onto a tilted, spinning mirror to create a circular scan. The scanned beam is then directed toward both eyes of a subject. The subject fixates on a target within the device, which centers the circle on the point of retinal fixation and focuses the laser light onto the retina during the scan. The light passes through the nerve fibers of the retina, and the light is altered by the retinal structure and

ocular alignment at the moment of the scan. Light is then retro-reflected by the fundus of the eye and returned through the optical system of the eye back to the opening of the instrument.

Viewing pathway: The returning light enters through the aperture of the device, passes back through the scanning mirror, and is then directed via a beam-splitter onto a knife-edge prism to separate the right and left eye signals. Each beam path is then directed onto right and left eye polarization analyzers. Changes in polarization are converted to an electrical signal and digitized for onboard analysis in software.

The software analysis begins with a computerized Fourier analysis of the digitized signal to identify frequency components. If the frequency of returning light for any one eye is determined to have doubled during its passage through the eye, central fixation of the fovea of that eye is confirmed. If central fixation is detected in both eyes simultaneously, the subject is said to have normal binocular alignment and normal binocular vision. If central fixation is not detected in one or both eyes, the subject is said to have strabismus (misaligned eyes) with reduced binocular vision and/or reduced visual acuity.

The results are conveyed to the operator through two LED indicator lights on the surface of the instrument. If the panel is illuminated with 2 green lights (normal binocular alignment) then the operator is advised to make a "pass" recommendation. If the panel indicates 1 red light (abnormal result – unilateral) or 2 red lights (abnormal results – bilateral), then the subject has reduced binocular vision and/or reduced visual acuity. In either case (1 or 2 red lights), the operator is advised to make a "refer" recommendation.

SUMMARY OF NONCLINICAL/BENCH STUDIES

ELECTRICAL SAFETY

The PVS was tested per the requirements of the IEC 60601-1: 2005 (3rd edition), Medical Electrical Equipment: General Requirements on Basic Safety and Essential Performance to provide reasonable assurance of the basic safety and essential performance of the device. The device is in conformance with the standard and passed applicable sub-clauses.

ELECTROMAGNETIC COMPATIBILITY (EMC)

The PVS was tested according to the IEC 60601-1-2:2007 (3rd edition), Medical Electrical Equipment - Part 1-2: General Requirements for Basic Safety and Essential Performance - Collateral standard: Electromagnetic Compatibility - Requirements and Tests to address EMC concerns for this device. All results demonstrated acceptable performance.

OPTICAL RADIATION SAFETY TESTING

All device light sources that direct optical radiation into or at the eye in the device, including the scanning laser, rangefinder laser, and fixation LED have been tested and

evaluated under worst case clinical exposure conditions and times for all intended uses and applications based on ISO 15004-2:2007. All light sources have been evaluated to be Group 1 and the emission for multiple source instruments at 2 hours and 8 hours have been evaluated. The device is a Group 1 Instrument per ISO 15004-2:2007 (1st edition).

The device was tested and evaluated per the IEC 60825-1:2007 (2nd edition) criteria. All results demonstrated acceptable performance. Data from the light safety for the laser diode sources (Scanning laser and Rangefinder laser) demonstrate that the PVS does not exceed Class I accessible emission limits (AELs) and is considered a Class I laser product per 21 CFR 1040.

Labeling, as necessary to claim compliance with IEC 60825-1:2007, is present on the device and user manuals.

SOFTWARE

The following device features are controlled by embedded firmware housed in the Central Processing Unit (CPU):

- User interface: Input from device buttons; display of output on Liquid Crystal Display (LCD) and LEDs.
- Fixation LED control: LED target for patient to fixate on.
- Laser drive and monitoring: The power level (up to hardware maximum) is controlled and monitored.
- Motor control and monitoring: The spinning motor is controlled and speed regulated (to display infrared light as a circle, incident on the retina).
- Photo sensors: Sampling from photo sensors (diodes).
- Non-volatile memory: Storing of information from previous scan (not permanent).
- Signal processing: Data collected from photo sensors is processed in the digital signal processor to allow for spectral analysis, and the resulting data is processed to determine the results of the scan.

A failure or latent flaw in the software for the PVS could indirectly result in minor injury to the patient or operator through incorrect or delayed information or through the action of a care provider. All of the elements of software documentation corresponding to the risk level of the software ("Moderate" Level of Concern as outlined in FDA's Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices) have been provided. Adequate documentation describing the software development procedures provide the foundation that the software will operate in a manner as described in the specifications. Hazard analysis was performed to characterize software risks including laser malfunction and measurement related errors. The following verification and validation (V&V) testing was conducted to address the potential hazards with satisfactory results: background and measurement data acquisition, calculation, and user interface tests.

PERFORMANCE TESTING – BENCH – LOWER LIMIT OF DETECTION

The PVS was tested to determine the lower limit of detection. A model patient was constructed consisting of two model eyes (each containing a refracting lens, iris aperture, and a birefringent retinal surface) positioned with normal binocular alignment at the prescribed testing distance. Once binocular alignment was detected with this configuration, prisms were placed in the light path to simulate deviation away from central fixation, and testing performed repeatedly to determine whether the device could detect misalignment. Degrees of deviation are converted to prism diopters using the formula b(4) Acceptance criteria for the testing was that the device will give "pass" results (60% binocularity or greater) when prisms inducing a deviation below the lower detection limit of the device are used and that the device will give "refer" results (<60% binocularity) when prisms inducing a deviation above the lower detection limit are in place. Testing was performed on a total of three total devices on both the left and right model eyes with 10 consecutive measurements for each. Prism powers from b(4)) Δ were used. The results of this testing are summarized below:

Table 2: Lower Detection Limit Bench Testing Results

Deviation in Prism Diopters (PD)	Deviation in degrees (α)	D1 – RE BIN (%)	D1 – LE BIN (%)	D2 – RE BIN (%)	D2 – LE BIN (%)	D3 – RE BIN (%)	D3 – LE BIN (%)
b(4)		100%	100%	100%	100%	100%	100%
		100%	100%	100%	100%	100%	100%
		100%	100%	60-100%	100%	100%	100%
		0%	0%	0%	0%	0%	0%
		0%	0%	0%	0%	0%	0%

D1, Device 1; D2, Device 2; D3, Device 3; RE, right eye; LE, left eye; BIN, binocularity score.

Lower limit bench testing demonstrated that the measured detection limit for the PVS is between b(4) Device 2, RE gave responses ranging from 60% - 100% at the detection limit (all considered "Pass" scores with average BIN score of 92%). All other devices gave responses of either 0% (for higher powered prisms) or 100% (for lower powered prisms) for each eye in all 10 trials. The slight variability in one device close to the detection limit might be expected as a result of very slight changes in motor speed, circuitry, or prism positioning.

PERFORMANCE TESTING – BENCH – PRECISION

The PVS was tested with a crossed design of three devices and three operators to determine the precision of measurements in model eyes with simulated bifoveal fusion, simulated strabismus at just above the lower detection limit of the device b(and simulated strabismus in patients with a clinically significant angle (b(4 1`) Ten prism diopters b(4) was chosen as a large enough angle to preclude development of binocular vision, while still small enough that the strabismus would not be grossly

obvious to a non-clinician. Testing was performed by naïve operators. Each operator obtained background, performed test, recorded results, and repeated for 10 consecutive trials with each device and condition. The following acceptance criteria were used:

1. Device will give consistent "pass" results (60% binocularity or greater) when no prism is in place (bifoveal fixation).
2. Device will give "refer" results (<60% binocularity) when prisms inducing a clinically significant deviation are in place.
3. Device will give "refer" results (<60% binocularity) when prisms inducing a deviation above the lower detection limit are in place.
4. In all cases (#1-3 above), results will be independent of device and operator with 90% consistency.

The results showed that no variability could be attributed to operator or device at each testing condition as summarized in Table 3:

Table 3: Bench Precision Testing Results

Testing condition		Device 1			Device 2			Device 3		
		Op1	Op2	Op3	Op1	Op2	Op3	Op1	Op2	Op3
Bifoveal fusion b(4)	BIN	100%	100%	100%	100%	100%	100%	100%	100%	100%
	Yield	100%	100%	100%	100%	100%	100%	100%	100%	100%
	Tries	5	5	5	5	5	5	5	5	5
Lower detection limit b(4)	BIN	0%	0%	0%	0%	0%	0%	0%	0%	0%
	Yield	100%	100%	100%	100%	100%	100%	100%	100%	100%
	Tries	5	5	5	5	5	5	5	5	5
Clinically significant angle b(4)	BIN	0%	0%	0%	0%	0%	0%	0%	0%	0%
	Yield	100%	100%	100%	100%	100%	100%	100%	100%	100%
	Tries	5	5	5	5	5	5	5	5	5

10 trials per cell; Op1, operator 1; Op2, operator 2; Op3, operator 3.

SUMMARY OF CLINICAL INFORMATION

Pivotal clinical trial

A pivotal clinical trial to determine the diagnostic accuracy of the device was conducted. The results of this trial provide a reasonable assurance of safety and effectiveness of the device for the indicated pediatric sub-population (age 2 to 8 years) and clinical environment (professional eye care settings).

This trial was a prospective, multi-center, observational investigation conducted at three clinical sites in the United States. Two of the sites are pediatric ophthalmology practices (clinic at a teaching hospital and a private practice). The third site is a comprehensive ophthalmology clinic. Eligible participants were tested with the PVS device, then underwent assessment by a reference standard (comprehensive eye examination, or "reference examination"). The reference examination was defined as a comprehensive ophthalmologic examination* performed by clinical teams (board-certified pediatric ophthalmologists, orthoptists, optometrists, and ophthalmic technicians).

The clinical conditions of interest were the following:
1. Amblyopia, defined as a visual acuity of worse than 20/40 and 2 logMAR-line difference between the two eyes;
2. Constant strabismus, defined as >2 prism diopters (PD) at near and or distance;
3. Intermittent strabismus, defined as strabismus that could be controlled intermittently either through fusional mechanisms or a compensatory head position.

The inclusion criteria were the following:
1. Age 2 to 8 years
2. Informed consent from parent or guardian.

The exclusion criteria were the following:
1. History of development delay or cognitive deficit;
2. Inability to complete the reference standard (comprehensive eye examination);
3. Obvious ocular abnormalities warranting specialist referral.

Participants were excluded from final data analyses for the following reasons:
1. Inability to cooperate or complete all elements of the reference examination;
2. Inability to cooperate for testing with the PVS device;
3. Other ocular conditions besides strabismus or amblyopia.

*The comprehensive examination consisted of the following elements:
- Visual acuity evaluation using whole line or crowding bars and age-appropriate methodology (Snellen letters when possible, otherwise an applicable alternative, including HOTV letters, LEA symbols, or CSM ["central, steady, and maintained"] assessment of fixation);
- Anterior segment evaluation performed with the slit-lamp biomicroscope or hand light (for younger ages or levels of cooperation);
- Evaluation of external ocular structures and for presence of ptosis (>1 mm of eyelid droop);
- Extraocular motility evaluation (performed prior to administration of cycloplegic agents), including measurement of strabismus (prism-and-cover test or Krimsky test) and assessment of whether the deviation is intermittent or constant. In cases where strabismus was detected, phoria was distinguished from tropia by the cover-uncover test;
- Evaluation of stereopsis (performed prior to visual acuity);
- Cycloplegic refraction with retinoscopy to identify the presence of hyperopia, myopia, anisometropia, or high amounts of astigmatism;
- Dilated fundus examination to assess for structural abnormalities of the retina of the eye, with focus on the fovea (the area scanned by the PVS).

Results of pivotal clinical trial

333 children were enrolled and data from 252 were included for analyses. No adverse events were reported. Enrollment characteristics are summarized in Tables 4 and 5.

Table 4: Disposition of enrolled participants

Enrollment Results	Site 1	Site 2	Site 3	Total
Received Informed Consent	33	111	189	**333**
Included into final analysis	26	74	152	**252**
Excluded from final analysis (explanation below)	7	37	37	**81**
Did not finish PVS test only	*5*	*0*	*1*	*6*
Did not finish Reference Exam only	*0*	*0*	*14*	*14*
Completed neither PVS test nor Reference Exam	*0*	*33*	*0*	*33*
PVS result missing only	*2*	*0*	*0*	*2*
Both PVS and Reference Exam results missing	*0*	*0*	*2*	*2*
Obvious ocular abnormalities	*0*	*4*	*20*	*24*
Grand Total Enrolled	**33**	**111**	**189**	**333**

Table 5: Demographic characteristics of cohort

Site	Age (mean, SD, median, min-max)	Gender (Male) x/n (%) (LCL, UCL)	Race x/n (%)
Site 1 (n=26)	5 (0.90) 5 (3, 6)	14/26 (53.8) (33.4, 73.4)	White 0/26 (0.0) Hispanic 0/26 (0.0) African Am. 0/26 (0.0) Asian 26/26 (100.0) Other 0/26 (0.0)
Site 2 (n=74)	5 (1.64) 5 (3, 8)	30/74 (40.5) (29.4, 51.7)	White 58/74 (78.4) Hispanic 1/74 (1.4) African Am. 7/74 (9.5) Asian 2/74 (2.7) Other 6/74 (8.1)
Site 3 (n=152)	4 (1.35) 4 (2, 6)	69/152 (45.4) (37.3, 53.7)	White 107/152 (70.4) Hispanic 19/152 (12.5) African Am. 10/152 (6.6) Asian 10/152 (6.6) Other 6/152 (3.9)
Total (n=252)	5 (1.45) 5 (2, 8)	113/252 (44.8) (38.7, 51.0)	White 165/252 (65.5) Hispanic 20/252 (7.9) African Am. 17/252 (6.7) Asian 38/252 (15.1) Other 12/252 (4.8)

Sensitivity and specificity of the PVS

The primary endpoints are sensitivity (SN) and specificity (SP) of the PVS device. Sensitivity was computed as the number of true positives (TP) divided by the number of participants determined by the reference examination to have amblyopia and/or strabismus. A TP is defined as the number of participants with a "refer" PVS result among those determined (by the reference examination) to have amblyopia and/or strabismus. Specificity was computed as the number of true negatives (TN) divided by the number of participants determined not to have amblyopia and/or clinically significant strabismus. A TN is defined as the number of participants with a "pass" PVS result among the participants determined (by the reference examination) not to have amblyopia and/or strabismus. Performance goals (PGs) of 80% and 82% for SN and SP,

respectively, were derived from the literature[1,2,3,4,5] and pre-specified. Secondary endpoints were positive and negative predictive value (PPV and NPV, respectively) of the PVS device. Positive Predictive Value (PPV) was computed as the number of TP divided by the number of participants determined to have a "refer" PVS result. Negative Predictive Value (NPV) was computed as the number of TN divided by the number of participants determined to have a "pass" PVS result. PGs for PPV and NPV were not pre-specified. Sub-group analyses were not pre-specified.

Observed prevalence of amblyopia and/or strabismus ranged from 11.5% to 78.4% across the three clinical sites.

Pooled and stratified (by site and age strata) results for SN, SP, PPV, and NPV are shown in Tables 6 and 7:

Table 6: Pooled and Stratified Results by Site

Site 1	**Test Result**	**Amblyopia/ Strabismus**	**No Amblyopia/ Strabismus**	**Total**
	Refer	3	1	4
	Pass	0	22	22
	Total	3	23	26
	Sensitivity = 100*3/3 = 100.0% (29.2 – 100.0%) Specificity = 100*22/23 = 95.7% (78.1 – 99.9%) PPV = 100*3/4 = 75.0% (19.4 – 99.4%) NPV = 100*22/22 = 100.0% (84.6 – 100.0%) Observed disease prevalence = 100* (3/26) = 11.54%			
Site 2	**Test Result**	**Amblyopia/ Strabismus**	**Not Amblyopia/ Strabismus**	**Total**
	Refer	49	3	52
	Pass	9	13	22
	Total	58	16	74
	Sensitivity = 100*49/58 = 84.5% (72.6 – 92.7%) Specificity = 100*13/16= 81.3% (54.5 – 96.0%) PPV = 100*49/52 = 94.2% (84.1 – 98.8%) NPV = 100*13/22 = 59.1% (36.4 – 79.3%) Observed disease prevalence = 100* (58/74) = 78.38%			
Site 3	**Test Result**	**Amblyopia/ Strabismus**	**Not Amblyopia/ Strabismus**	**Total**
	Refer	75	5	80
	Pass	7	65	72
	Total	82	70	152
	Sensitivity = 100*75/82 = 91.5% (83.2 – 96.5%) Specificity = 100*65/70 = 92.9% (84.1 – 97.6%) PPV = 100*75/80 = 93.8% (86.0 – 97.9%) NPV = 100*65/72 = 90.3% (81.0 – 96.0%) Observed disease prevalence = 100* (82/152) = 53.95%			

[1] Vision in Preschoolers (VIP) Study Group. Optom Vis Sci 2009;86(6):619-23.
[2] Salcido AA et al. J AAPOS 2005;9:114-20.
[3] Arnold RW et al. Am Orthop J 2006;56:15-21.
[4] Leman R et al. J Sch Nurs 2006;22:237-43.
[5] Zaba JN et al. Optometry 2007 Oct;78(1):514-22.

Grand Total	Test Result	Amblyopia/ Strabismus	Not Amblyopia/ Strabismus	Total
	Refer	127	9	136
	Pass	16	100	116
	Total	143	109	252
	Sensitivity = 100*127/143 = 88.81% (82.47 – 93.47%) Specificity = 100*100/109 = 91.74% (84.90 – 96.16%) PPV = 100*127/136 = 93.38% (87.81 – 96.93%) NPV = 100*100/116 = 86.21% (78.57 – 91.91%) Observed disease prevalence = 100* (143/252) = 56.75%			

Table 7: Pooled and Stratified Results by Age Strata

AGE (yr)	Test Result	PPV/NPV	Disease Prevalence
2 (n=20)	Sensitivity = 100*13/15 = **86.67%** Specificity = 100*5/5 = **100.0** %	PPV = 100*13/13 = **100.0%** NPV = 100*5/7 = **71.43%**	75%
3 (n=51)	Sensitivity = 100*28/31 = **90.32%** Specificity = 100*18/20= **90.0** %	PPV = 100*28/30 = **93.33%** NPV = 100*18/21 = **85.71%**	61%
4 (n=49)	Sensitivity = 100*29/34 = **85.29%** Specificity = 100*12/15 = **80.0%**	PPV = 100*29/32 = **90.63%** NPV = 100*12/17 = **70.59%**	69%
5 (n=64)	Sensitivity = 100*20/23 = **86.96%** Specificity = 100*38/41 = **92.68** %	PPV = 100*20/23 = **86.96%** NPV = 100*38/41 = **92.68%**	36%
6 (n=52)	Sensitivity = 100*24/26 = **92.31%** Specificity = 100*25/26= **96.15%**	PPV = 100*24/25= **96.0%** NPV = 100*25/27 = **92.59%**	50%
7-8 (n=16)	Sensitivity = 100*13/14 = **92.86%** Specificity = 100*2/2 = **100.0%**	PPV = 100*13/13 = **100.0%** NPV = 100*2/3 = **66.67%**	88%

The sub-analysis of clinical outcomes by age was not pre-specified and therefore should be considered exploratory.

False Negatives and False Positives

A False Negative (FN) is defined as a participant with a "pass" PVS result among those determined by the reference examination to have amblyopia and/or strabismus. A False Positive (FP) is defined as a participant with a "refer" PVS result among those determined (by the reference examination) not to have amblyopia and/or strabismus. Of the 252 enrolled patients who completed the study, there were nine FP and 16 FN. Of the nine FPs, two had risk factors (anisometropia) and two had astigmatism. The others had no known risk factors or other abnormalities. Of the 16 FNs, six had intermittent or accommodative esotropia, three had intermittent exotropia, two had non-intermittent esotropia, two had amblyopia without strabismus, two had esotropia and amblyopia, and one had bilateral amblyopia.

Reasons for Study Exclusion

Site 1:

- Five participants were deemed unable/unwilling to cooperate for the PVS scan.
- Two participants were excluded as a result of study error
    - One study error was a result of the PVS user not recording an output

- One study error was a result of the site's inability to match participant's study ID number to a reference examination

Site 2:

- Thirty-three participants had site IDs created, but there were no corresponding PVS or reference examination data generated.
- Four participants had exclusion criteria (gross structural defects of the eye warranting referral to an ophthalmologist without screening) discovered during reference examination
  - One participant had a cataract
  - One participant had Axenfeld Reiger anomaly
  - One participant had a corneal scar
  - One participant had a chalazion

Site 3:

- Twenty participants had grossly visible ocular abnormalities warranting referral including media opacities, ptosis, and conjunctivitis.
  - One of the twenty had developmental delay
  - One of the twenty had recent strabismus surgery
- Fourteen participants did not have a cycloplegic refraction available the day of the visit
- Two had PVS testing performed but no PVS output recorded
- One participant was unable/unwilling to cooperate and maintain head control during the PVS scan.

Twenty four (24) of the 81 (29.6%) excluded participants had other referable ocular conditions. Of these 24 participants, 15 (62.5%) received a "refer" result from the PVS and 9 of the 24 (37.5%) received a "pass" result from the PVS as summarized in Table 8.

Table 8: Clinical Condition Analysis for FN and FP with Obvious Ocular Abnormalities

Reference Examination Diagnosis	**PVS Result**	
	Refer	**Pass**
Anisocoria and photophobia	1	-
Axenfeld-Rieger anomaly	1	-
Blepharitis	1	2
Cataract, not otherwise specified	-	1
Cataract, anterior polar	-	1
Cataract, posterior subcapsular	1	-
Chalazion	1	-
Conjunctivitis	2	1
Corneal scar	1	-
Developmental delay	1	-
Lid hemangioma	1	-
Nasolacrimal duct obstruction	1	3
Neurofibromatosis	-	1
Ptosis	1	-
Recent strabismus surgery	1	-

Reference Examination Diagnosis	PVS Result	
	Refer	Pass
Uveitis	2	-
Total	**15**	**9**

These results show that PVS has a sensitivity of 89% and specificity of 92% when used in professional eye care settings. These results meet and exceed the pre-specified performance goals for sensitivity and specificity. They demonstrate a reasonable assurance of safety and effectiveness.

LABELING

The labeling (user manual) is sufficient and meets the requirements of 21 CFR 801.109. The user manual contains the Indications for Use, summary device description (including hardware and software overviews), warnings and precautions, instructions for use, instructions for device maintenance, troubleshooting instructions, information related to electromagnetic compatibility, optical radiation classification and summaries of performance testing.

Physical labeling of the device includes all key operating features of the device user interface, (e.g., buttons, LED outputs, screen display).

RISKS TO HEALTH

Table 9 identifies the risks to health that may be associated with use of Strabismus Detection Device and the measures necessary to mitigate these risks.

Table 9: Identified Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measure
Diagnostic Risks (False Positives, False Negatives, No output)	• Clinical Performance Testing • Non-Clinical Performance Testing • Software Verification, Validation and Hazard Analysis • Labeling
Electromagnetic Interference with Other Devices	• Electromagnetic Compatibility (EMC) Testing • Labeling
Electrical Shock	• Electrical Safety Testing • Labeling
Ocular Light Toxicity	• Optical Radiation Safety Testing • Software Verification, Validation and Hazard Analysis • Labeling
Use Error	• Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the Strabismus Detection Device is subject to the following special controls:

1. Clinical performance testing must demonstrate the device performs as intended under anticipated conditions of use. Testing must be conducted in a representative patient population and clinical setting for the indicated use. Demonstration of clinical performance must include assessment of sensitivity and specificity compared to a clearly defined reference standard (comprehensive ophthalmological examination comprises age-appropriate visual acuity testing, examination of the external ocular adnexae and orbit, anterior segment evaluation, extraocular motility evaluation, assessment of stereopsis, cycloplegic refraction, and dilated fundus examination).

2. Non-clinical performance testing must demonstrate the device performs as intended under anticipated conditions of use. The following technical characteristics must be evaluated:
    a. Verification of lowest detectable amount of deviation.
    b. Validation of the accuracy and precision at the lowest detectable amount of deviation.

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

4. Optical radiation safety testing must demonstrate the device is safe per the directions for use.

5. Performance testing must demonstrate the electromagnetic compatibility of the device.

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

7. Labeling must include the following:

    a. Summaries of non-clinical and clinical performance testing.
    b. Instructions on how to correctly use and maintain the device.
    c. Instructions and explanation of all user-interface components.
    d. Information related to electromagnetic compatibility and optical radiation classification.

BENEFIT/RISK DETERMINATION

The primary risks of the device are false negatives and false positives. False negative results may lead to a delay in amblyopia diagnosis. This increases the risk for permanent vision loss in false negative individuals. The earlier in age a child is diagnosed and treated for amblyopia, the more likely the child can preserve vision. False positive results subject children to unnecessary eye examinations, causing inconvenience to caretakers and unnecessary anxiety to children. Unnecessary referrals also waste resources and time.

The probable benefits of the device are based on the data collected in the clinical studies described above. They are also based on data collected from non-clinical precision testing. The sponsor has demonstrated that the PVS device performs well in a referral pediatric population (those being evaluated in eye care clinics) ages 2 to 8, with sensitivity and specificity (lower bounds of the 95% confidence intervals) of 82.47% and 91.74%, respectively. Non-clinical performance testing has demonstrated that the lower detection limit of the PVS is between 1.5 to 2 prism diopters (PD), which matches or exceeds the lower detection limit of current clinical examination methods. Non-clinical performance testing on model eyes also demonstrated that the PVS has repeatable results around the lower detection limit. The benefit of the PVS device is that amblyopia and/or clinically significant strabismus may be identified earlier, particularly in toddlers (ages 2-3), as testing with the PVS in this age group does not require as much patient cooperation as visual acuity testing and is likely more accurate than a cursory penlight examination alone. Earlier detection and tertiary referral, when necessary, would allow treatment in a timelier manner. More timely treatment is more likely to be successful, which in turn could result in decreased childhood incidence of permanent vision loss. When patients have limited cooperation for a full eye exam, the PVS would be useful to eye care professionals. In such cases, an eye care professional may use the PVS results in conjunction with the totality of all available clinical information from a patient to make a more informed management decision (e.g., tertiary referral, repeat examination, etc.).

Patient Perspectives

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

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that for the screening of amblyopia and microstrabismus associated with amblyopia in children age 2 to 8 undergoing evaluation in a professional eye care setting and who are responsive to taking direction and who can pay attention for at least 5 seconds, the probable benefits outweigh the probable risks for the PVS. The device provides substantial 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 Pediatric Vision Scanner is granted and the device is classified under the following:

Product Code: PMW
Device Type: Strabismus Detection Device
Class: II
Regulation: 21 CFR 886.1342