DE NOVO CLASSIFICATION REQUEST FOR EYEBOX

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Traumatic brain injury eye movement assessment aid. A traumatic brain injury eye movement assessment aid is a prescription device that uses a patient's tracked eye movements to provide an interpretation of the functional condition of the patient's brain. This device is an assessment aid that is not intended for standalone detection or diagnostic purposes.

NEW REGULATION NUMBER: 21 CFR 882.1455

CLASSIFICATION: Class II

PRODUCT CODE: QEA

BACKGROUND

DEVICE NAME: EyeBOX

SUBMISSION NUMBER: DEN170091

DATE DE NOVO RECEIVED: December 22, 2017

CONTACT: Oculogica, Inc.
33 Irving Place
New York, New York 10003

INDICATIONS FOR USE

The EyeBOX is intended to measure and analyze eye movements as an aid in the diagnosis of concussion within one week of head injury in patients 5 through 67 years of age in conjunction with a standard neurological assessment of concussion.

A negative EyeBOX classification may correspond to eye movement that is consistent with a lack of concussion.

A positive EyeBOX classification corresponds to eye movement that may be present in both patients with or without concussion.

LIMITATIONS

For prescription use only.

The EyeBOX device should not be used as a standalone assessment of concussion.

The safety and effectiveness of the EyeBOX device has not been established in patients suspected of having moderate or severe TBI, including patients with a Glasgow Coma Scale score less than 13 and patients with evidence of structural injury or intracranial hemorrhage as determined by imaging modalities.

The safety and effectiveness of the EyeBOX device has not been established in patients who have incurred an injury more than 1 week before assessment with the EyeBOX.

The safety and effectiveness of the EyeBOX device has not been established in patients who have any of the following:

- Have visual acuity worse than 20/80
- Have a history of disordered eye movement (including strabismus, diplopia, and amblyopia)
- Have conditions that affect the eye tissue, including retinal degeneration, cataracts, and corneal scarring
- Have abnormal function of cranial nerves III, IV, or IV
- Are intoxicated or are under the influence of medication, drugs, or alcohol
- Have attention deficit hyperactivity disorder

The EyeBOX should only be used by physicians or under the direction of physicians who have been trained to use the device.

The device should not be used as a substitute for a CT scan or as a stand-alone diagnostic device.

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

DEVICE DESCRIPTION

The Oculogica EyeBOX system consists of an integrated stand, eye-tracking camera, video stimulus display screen, and computer programmed for analysis of eye movements. It is intended to detect abnormal eye movement that may be related to a concussion. The device measures gaze, calculates a score on a 0-20 scale based on these measurements, and displays an EyeBOX classification based upon whether the scale value is above 10 or not. Scale values of 10 or more yield a positive EyeBOX classification, while scale values under 10 yield a negative EyeBOX classification.

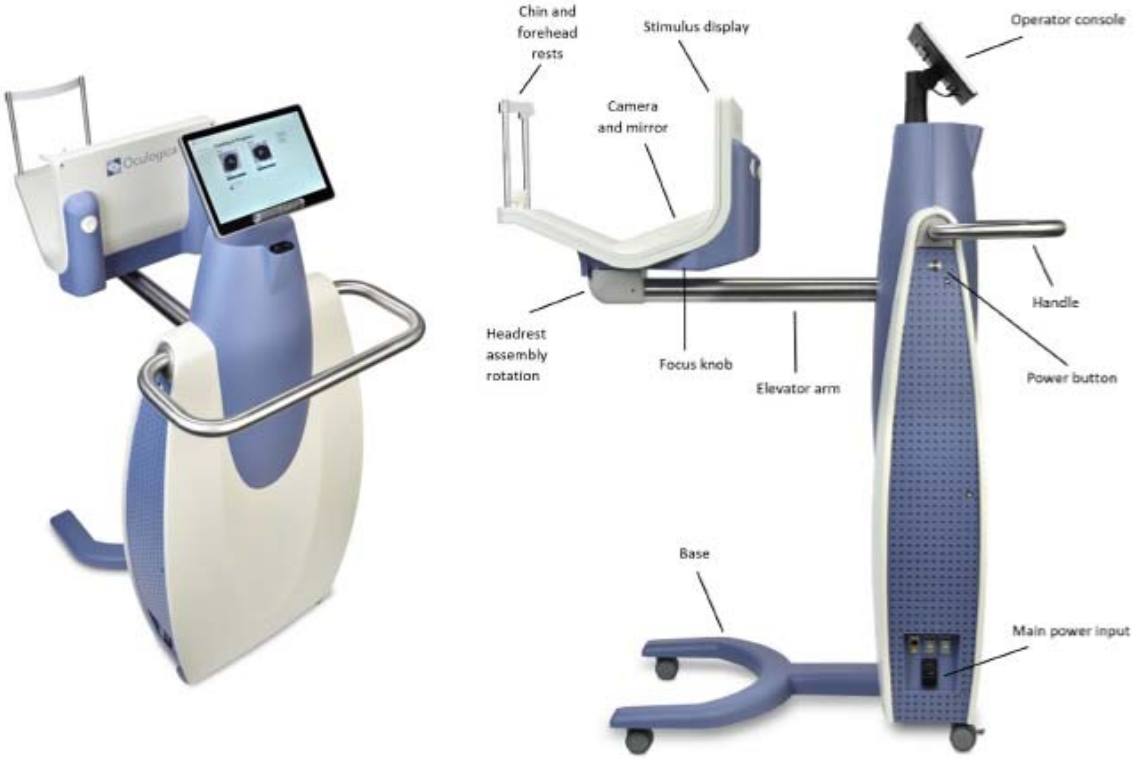

Figure 1: Oculogica EyeBOX device

Eye-tracking camera

The device eye-tracking camera detects eye motion events and computes the gaze coordinates for each eye over a period of 220 seconds. The camera is a commercially available system that uses an infrared illumination technique to capture 500 frames of gaze data per second for each eye to track the movement of the pupil. Patient-specific calibration is not used for tracking of pupillary movement.

Stimulus screen

The stimulus screen is used to display a video that lasts 220 seconds. The video is one of several pre-determined videos that may be selected. These videos include music videos, clips from children's movies, sports clips, talent performances, and other television clips. The video aperture is square, approximately one ninth the size of the LCD screen; one third each area dimension resulting in one ninth total stimulus screen area. The trajectory around the Stimulus Screen follows a predefined discrete path of 5 cycles along the perimeter of the stimulus screen.

Software analysis

During eye tracking, EyeBOX collects 220 seconds of binocular gaze data at 500Hz as the patient watches the video stimulus go around the screen five times. The first and last ten seconds of data are discarded. The data are processed for blinks and normalized. A score between 0 and 20 is the calculated from the normalized data. Scores of 10 or more are presented as consistent with the possible presence of concussion.

Figure 2, below, shows a sample clinical report for a normal patient. The five plot pairs on the left-hand side (L1 through R5) are the left and right eye tracking for each of the five cycles as the eyes follow the aperture around the monitor. The two plots at the top right (L1-5 and R1-5) are all five cycles for the left and right eye superimposed. The two boxes below that (L Avg and R Avg) are the averages of five cycles. The three line plots on the lower right are the differences in the x direction for the left and right eye, the differences in the y direction for the left and right eye, and an overlay plot of the individual left and right x and y plots on the same timeline.

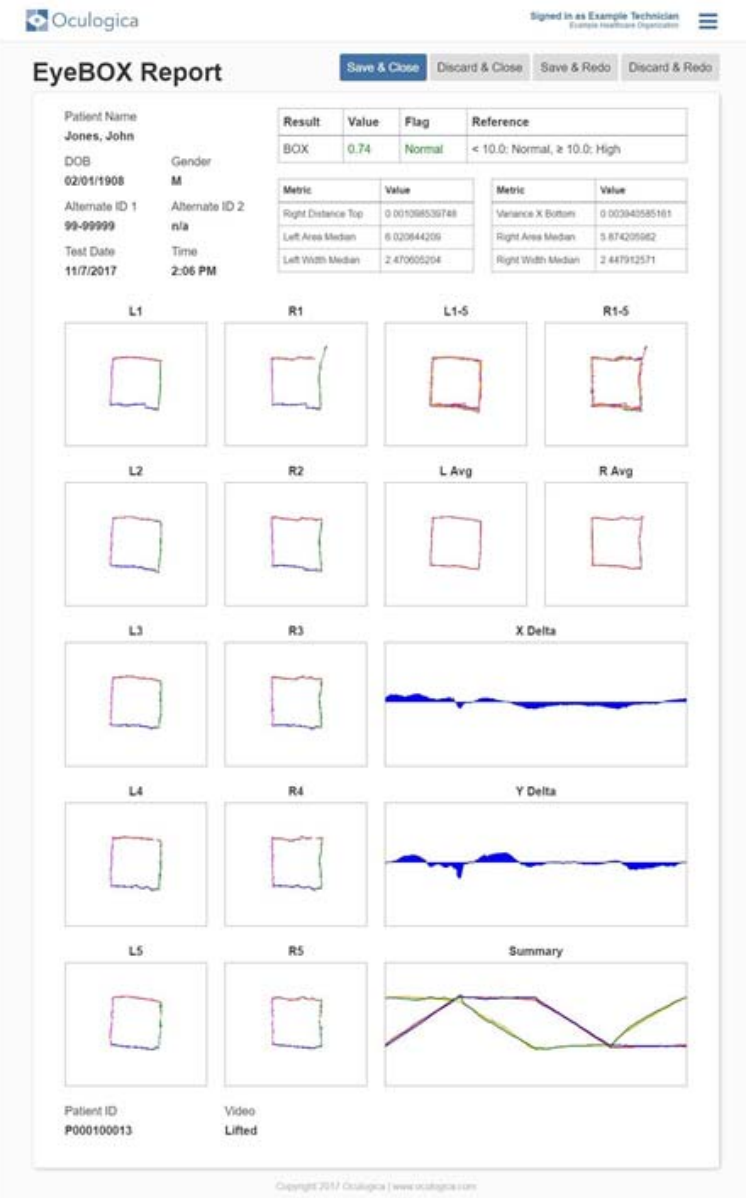

Figure 2: EyeBOX clinical report

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The device does not have patient-contacting materials because the device is intended for use with biocompatible drapes for the patient chinrest and headrest. Therefore, a full biocompatibility evaluation according to ISO 10993-1 was not needed in accordance with the FDA 2016 Guidance Document *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process."*

STERILITY

The device is provided non-sterile. Cleaning instructions are provided in the user manual.

ELECTROMAGNETIC CAPABILITY & ELECTROMAGNETIC SAFETY

Performance testing was conducted to demonstrate conformance to the following standards:

- ANSI/AAMI ES60601-1: 2005 and A1:2012, *Medical electrical equipment Part 1: General requirements for basic safety and essential performance*

- IEC 60601-1-2:2014 (4th edition), *Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral Standard: Electromagnetic Compatibility – Requirements and Tests*

Modifications were made to the device to conform to the requirements of EN 61000-4-2:2008, *Electrostatic Discharge Immunity* by adding a non-conductive coating to the device power button to mitigate the risks of device shutdown after electrostatic discharge. Marketed versions of the device (b) (4)

SOFTWARE

A failure or latent flaw in the software for the EyeBOX could indirectly result in patient injury; therefore, the software of this device is considered to have a "Moderate" level of concern. The submission contained all the elements of software documentation corresponding to the "Moderate" level of concern, as outlined in the FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices." Adequate documentation describing the software, firmware, software specifications, architecture design, software development environment, traceability, revision level history, and unresolved anomalies provide the foundation for the conclusion that the software will operate in the manner described in the specifications. Hazard analysis characterized software risks including device malfunction and measurement-related errors. The submission describes verification and

validation testing to address the potential hazards with satisfactory results. The analysis algorithm was provided describing how the data are collected, how the data are pre-processed (including artifact removal and normalization), the underlying model that is applied to the processed data, and how the final device output(s) are calculated from the processed data.

PERFORMANCE TESTING - BENCH

Testing was performed to demonstrate conformance with the following standards:

- IEC 62471:2006 *Photobiological Safety of Lamps and Lamp Systems*
- ISO 15004-2:2007 *Ophthalmic Instruments - Fundamental Requirements and Test Methods Part 2: Light Hazard Protection*

SUMMARY OF CLINICAL INFORMATION

Study overview

In the pivotal clinical study, EyeBOX results were compared to a trial-specific clinical reference standard for concussion because there is no "gold standard" method to diagnose concussion. Initially, a 3-clinician panel was the clinical reference standard. Because 84.4% of the first N=199 adjudications had at least one clinician render a recommendation of "uncertain" for the patient's concussion status, investigators became concerned that the resulting clinical reference standard would not be interpretable. At this point in the study, they revised the clinical reference standard. Using the revised standard, a subject had a concussion if they exhibited (a) alteration of consciousness (AOC) or altered mental status (AMS) and scored less than 23 on the SCAT 3 Standardized Assessment of Concussion (SAC) and greater than 25 on the SCAT3 Symptom Severity Score (SSS), or (b) if they did not exhibit AOC/AMS but scored SAC<15 and SSS>32 on the SCAT 3. The presence of AOC/AMS was based on any of the following: self-report, witness report or the following responses to the SCAT3 SSS: "Difficulty Remembering" ≥ 4 or "Confusion" ≥ 4; or Child-SCAT3: "I get confused" ≥ 2 or "I forget things" ≥ 2. The results of the device output remained blinded for analysis when the reference standard was changed and remained blinded until the final study analysis.

N=293 subjects who were screened met the study inclusion criteria. Of these subjects, 10 were excluded from analysis because the user did not save the eye-tracking scan and one subject was excluded because of missing concussion symptom question responses. There are complete data for analysis from 282 enrolled subjects assessed with the device within 2 weeks of injury; however, 263 of the 282 subjects were assessed with the device within 1 week of injury, yielding insufficient evidence of device effectiveness beyond 1 week after injury.

Inclusion criteria

1. Ages 4 through 67 years (inclusive).
2. Diagnosis of traumatic brain injury with a potential for concussion.

3. Baseline vision correctable to within 20/500 bilaterally.
4. No prior history of diagnosed ocular motility disorder.
5. Able to provide a complete ophthalmologic, medical, and neurologic history and to list any medications, non-prescribed drugs, or alcohol consumed within the 24 hours prior to tracking.

Exclusion criteria

1. Penetrating head trauma.
2. CT scan determined by the attending radiologist to demonstrate evidence of acute brain injury including subdural, epidural or intraparenchymal hemorrhage, edema, or mass effect.
3. Burns, anoxic injury, multiple injuries, or extensive injuries resulting in medical, surgical, or hemodynamic instability.
4. Prior history of ocular motility dysfunction.
5. Prior extensive eye surgery.
6. Physical or mental injury or baseline disability rendering task completion difficult.
7. Intoxicated or have blood alcohol level greater than 0.2.

Co-primary effectiveness endpoint

The primary endpoint of the study is the sensitivity and specificity of the device in discriminating the presence or absence of concussion in head-injured patients per the eligibility criteria above. A lower one-sided 95% confidence limit greater than 70% for sensitivity and a lower one-sided 95% confidence limit greater than 70% for specificity were defined as the pre-specified performance goals. These goals were not met in the pivotal clinical study. To supplement the primary analysis, post-hoc analyses of positive predictive value (PPV) and negative predictive value (NPV) were conducted without defined performance goals. Although the primary endpoint was not met, the effectiveness analyses described above demonstrated that the probable benefit of the device outweighs the probable risk, as discussed in the Benefit-Risk Determination section below.

Results

No adverse events (device-related or unrelated) were reported in the study.

Of the 282 subjects included in the study analysis, 46 met the revised clinical reference standard definition of concussion. The EyeBOX identified 37 of these as positive for concussion (score 10 or higher), resulting in a measured sensitivity of 80.4% (66.1%, 91.9%). This corresponds to a False Negative Rate (FNR) of 19.6% (9/46). Of the 236 subjects who did not meet the clinical reference standard definition of concussion, EyeBOX identified 156 as negative for concussion (score less than 10) resulting in a measured specificity of 66.1% (59.7%, 72.1%).

EyeBOX Classification	Clinical Classification		Total
	Concussion	No Concussion	
Positive	37	80	117
Negative	9	156	165
Total	46	236	282

Table 1. Classification results of the EyeBOX device versus Clinical Classification

The negative predictive value (NPV) of the device was 94.5% (89.9%, 97.5%). The positive predictive value (PPV) was 31.6% (23.3%, 40.9%). For PPV and NPV reference, the study prevalence of clinical classification of concussion was 16.3% (46/282). Observed device performance in pediatric patients was comparable to the observed performance in adults. A summary of the device performance measures is provided in Table 2 below.

	All patients	Adults > 21 years old	Pediatrics ≤ 21 years old
Patients	**282**	(b) (4)	
Concussions	**46**		
Prevalence	**16.3%**		
Sensitivity (95% CI)	**80.4%** (66.1% - (b) (4)		
Specificity (95% CI)	**66.1%** (59.7% - 72.1%)		
PPV (95% CI)	**31.6%** (23.3% - 40.9%)		
NPV (95% CI)	**94.5%** (89.9% - 97.5%)		

Table 2: Summary of clinical performance

Test-retest reliability

The Bland-Altman analysis – a measure of test-retest reliability – for the device score from 0-20 (EyeBOX Score) is shown in the Figure 3 below, along with Bland-Altman analysis plots for two critical components of the EyeBOX Score in Figure 4. The proportion of equivalent outcomes (i.e., both tests result in a EyeBOX score ≥ 10, or both tests results in a EyeBOX score < 10) was 79.3% (95% CI 67.8-87.5%).

Cronbach's Alpha of the EyeBOX score for n=63 subjects was 0.79, (95% CI 0.69-0.89). Cronbach's Alpha and the proportion of equivalent outcomes for the EyeBOX score are shown in Table 2 below.

The Cronbach's Alpha of the critical components of the EyeBOX score for n=63 subjects was 0.69 (0.54, 0.84) and 0.88 (0.83, 0.94).

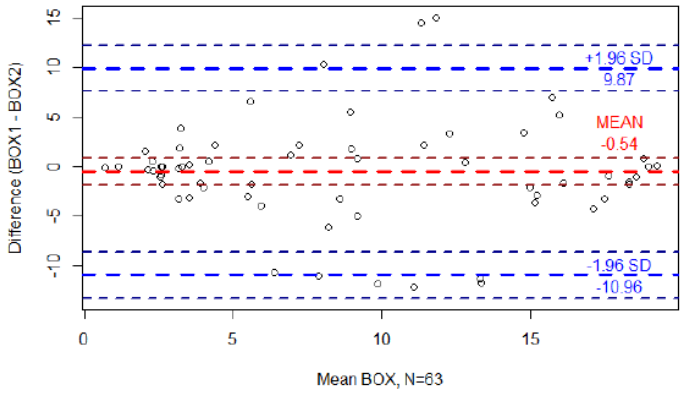

Figure 3: Bland-Altman analysis of EyeBOX score in N=63 patients

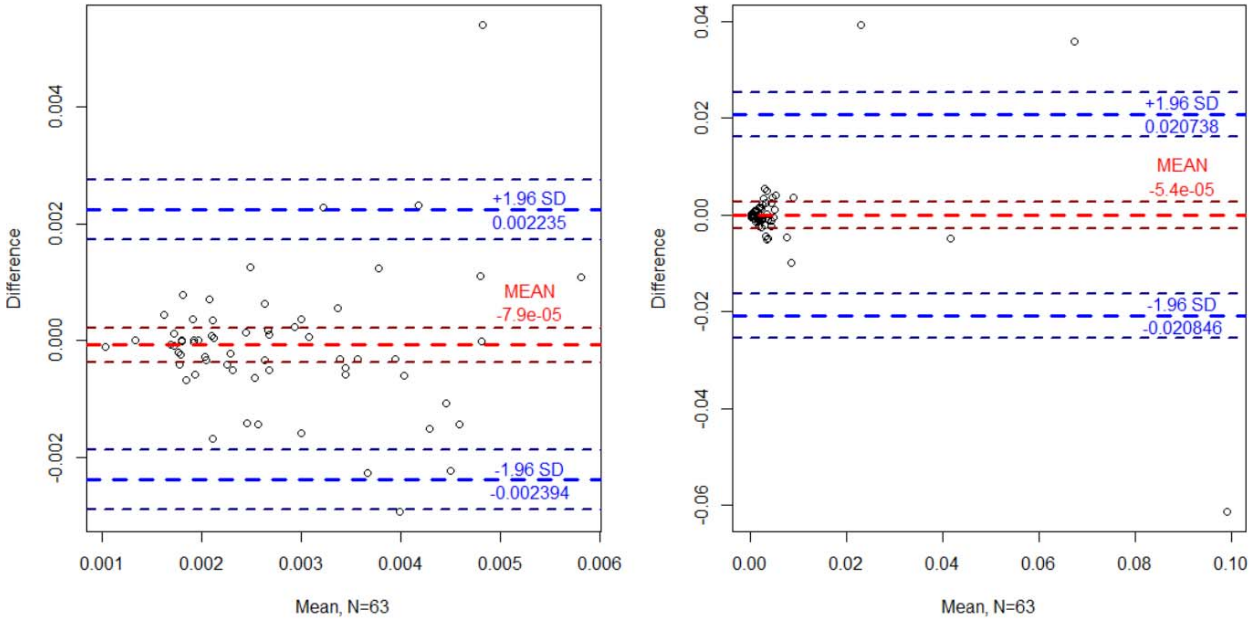

Figure 4: Bland-Altman analysis of critical component measurements of EyeBOX score in N=63 patients

Group	Proportion of Equivalent Outcomes (95% CI)	Cronbach's Alpha of BOX Score (95% CI)
All Test-Retest Subjects (N=63)	79.3% (67.8%, 87.5%)	0.79 (0.69, 0.89)

Table 3: Proportion of equivalent outcomes and Cronbach's Alpha of EyeBOX Score

Pediatric Extrapolation

Clinical data were collected in (b) (4) pediatric patients to support safe and effective use in pediatric patients age 5-21. The 95% confidence intervals for pediatric sensitivity, specificity,

positive predictive value, and negative predictive value overlapped with the corresponding adult performance values as shown in Table 2 above. Extrapolation is not necessary.

LABELING

User manual labeling was provided that:

- States that the device is not intended to represent a standalone diagnosis and other caveats for device use and interpretation of its results.
- States that not all patients with concussion will have eye tracking abnormalities.
- Identifies the visual acuity levels for which the device is intended to be used.
- Describes the clinical study performed with the device, including a description of the clinical reference standard and a description of the sensitivity, specificity, positive predictive value, and negative predictive value reported in the clinical study.
- Describes the test-retest reliability of the device, including Bland-Altman analysis plots.
- Describes how the test administrator and user should interact with the device.
- Includes a sample clinical report.
- Describes the electromagnetic compatibility (EMC) environment for use.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the traumatic brain injury eye movement assessment aid and the measures necessary to mitigate these risks.

Identified Risks to Health	Mitigation Measures
Incorrect or misinterpreted results, including: • False positive: brain injury when in fact none is present • False negative: no brain injury when in fact brain injury is present	Clinical performance testing; Software verification, validation, and hazard analysis; and Labeling
Interference with other devices	Electromagnetic compatibility (EMC) testing; and Software verification, validation, and hazard analysis
Electrical shock or burn	Electrical safety testing; and Software verification, validation, and hazard analysis
Adverse tissue reaction	Biocompatibility evaluation
Eye hazard or injury	Light hazard assessment

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the traumatic brain injury eye movement assessment aid is subject to the following special controls:

(1) Clinical performance data under anticipated conditions of use must evaluate tracked eye movement in supporting the indications for use and include the following:
   (i) Evaluation of sensitivity, specificity, positive predictive value, and negative predictive value using a reference method of diagnosis;
   (ii) Evaluation of device test-retest reliability; and
   (iii) A description of the development of the reference method of diagnosis, which may include a normative database, to include the following:
      (A) A discussion of how the clinical work-up was completed to establish the reference method of diagnosis, including the establishment of inclusion and exclusion criteria; and
      (B) If using a normative database, a description of how the "normal" population was established, and the statistical methods and model assumptions used.

(2) Software verification, validation, and hazard analysis must be performed. Software documentation must include a description of the algorithms used to generate device output.

(3) Performance testing must demonstrate the electrical safety and electromagnetic compatibility (EMC) of the device.

(4) The patient-contacting components of the device must be demonstrated to be biocompatible.

(5) A light hazard assessment must be performed for all eye-tracking and visual display light sources.

(6) Labeling must include:
   (i) A summary of clinical performance testing conducted with the device, including sensitivity, specificity, positive predictive value, negative predictive value, and test-retest reliability;
   (ii) A description of any normative database that includes the following:
      (A) The clinical definition used to establish a "normal" population and the specific selection criteria;
      (B) The format for reporting normal values;
      (C) Examples of screen displays and reports generated to provide the user results and normative data;
      (D) Statistical methods and model assumptions; and
      (E) Any adjustments for age and gender.
   (iii) A warning that the device should only be used by trained healthcare professionals;
   (iv) A warning that the device does not identify the presence or absence of traumatic brain injury or other clinical diagnoses;
   (v) A warning that the device is not a standalone diagnostic; and
   (vi) Any instructions to convey to patients regarding the administration of the test and collection of test data.

BENEFIT-RISK DETERMINATION

The risks of the device are based on data collected in the clinical study described above.

No device related serious or non-serious adverse events occurred in the clinical study.

The major risk of the EyeBOX device is a false negative result. Clinical trial results suggest a false negative report from the device would be expected in approximately 20% of patients and could result in a patient with a true concussion continuing activities that could result in further patient harms including an increased risk of persistent post-concussive symptoms or a second concussion. Cumulative head injury exposure may result in long-term brain damage. The risk of a false negative report is that a patient would develop a false sense of safety and continue activities with increased risk of cumulative head injuries.

These risks are mitigated by using this device as part of a multimodal evaluation, which includes history of mild head injury, injury details, and the current signs and symptoms on examination. The EyeBOX results should not be used as the sole measure to diagnose or exclude concussion and is not intended to be used in patients with moderate or severe injury.

The probable benefits of the device are also based on data collected in the clinical study as described above.

Compared to a reference standard to evaluate for the presence or absence of concussion, the device had a sensitivity of 80.4% (37/46) and a specificity of 66.1% (156/236). In the population studied, negative predictive value (NPV) was 94.5% (156/165) and positive predictive value (PPV) was 31.6% (37/117). The false negative rate was 19.6%. The benefit of an EyeBOX evaluation is an objective assessment of eye movements to supplement existing neurocognitive assessments as an aid in diagnosis of concussion. This benefit is of sufficient magnitude to serve as an additional assessment to help determine the presence of eye movement abnormalities that suggest brain injury and may help identify higher risk subjects to provide education to the patient that has been shown to be of prognostic benefit. An objective measure of brain injury may benefit an individual patient by providing additional motivation to avoid future head injury; however, a negative result should be interpreted by the clinician with caution and in the context of other concussion assessments because the consequences of a missed diagnosis may include persistent symptoms and increased risk of additional and cumulative head injury. Devices that aid in the assessment of concussion may help reduce the number of head injuries by providing objective evidence of brain injury that is otherwise not apparent to the patient.

Data for use in pediatric patients did not show performance differences between the populations as summarized previously in Table 2-(b) (4)

Additional factors to be considered in determining probable risks and benefits for the EyeBOX include:

a. The performance goals for the device were not met in the pivotal clinical study. The device's use as an adjunct to established methods for evaluation of concussion and high

negative predictive value (limiting the number of false negative results) were deemed acceptable to mitigate the risks of using the device as an aid in the assessment of concussion.

b. Although positive results by the device that did not coincide with clinical signs or symptoms of neurological injury were considered false positives, there is a large amount of uncertainty in the clinical adjudication of concussion as demonstrated in the study, thus raising the question as to whether these outcomes were truly false positives. This uncertainty in clinical adjudication may have similar implications for the reported false negative rate.
c. The test-retest reliability of the EyeBOX as shown in Table 2 and Figure 3 demonstrated some variability in the EyeBOX score output when tested twice in the same patient. However, the level of variability was determined to be adequately mitigated by (1) the device's performance in the pivotal clinical study, (2) labeling that described the test-retest reliability to the user, and (3) comparable test-retest reliability to medical devices and products that are currently legally marketed for the assessment of head injury.
d. Few alternative quantitative methods exist for aiding in the assessment of incident concussion. Quantitative methods that do not rely on patient-self reporting of symptoms could aid the clinician by providing a more objective assessment of the signs of concussion.

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, for the following indications for use statement:

> The EyeBOX is intended to measure and analyze eye movements as an aid in the diagnosis of concussion within one week of head injury in patients 5 through 67 years of age in conjunction with a standard neurological assessment of concussion.
>
> A negative EyeBOX classification may correspond to eye movement that is consistent with a lack of concussion.
>
> A positive EyeBOX classification corresponds to eye movement that may be present in both patients with or without concussion.

The probable benefits outweigh the probable risks for the EyeBOX. The device provides benefits and the risks can be mitigated using general controls and the identified special controls.

CONCLUSION

The De Novo request for the EyeBOX is granted and the device is classified as follows:

Product Code: QEA
Device Type: Traumatic brain injury eye movement assessment aid
Regulation Number: 21 CFR 882.1455
Class: II