510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:
k083184

B. Purpose for Submission:
Clearance of a new device

C. Measurand:
Tear Osmolarity

D. Type of Test:
Tear osmolarity through an electrical impedance measurement

E. Applicant:
OcuSense, Inc.

F. Proprietary and Established Names:
TearLab Osmolarity System

G. Regulatory Information:

1. Regulation section:
   21 CFR § 862.1540 Osmolality Test System
   21 CFR § 862.1660, Quality Control Material
2. Classification:
   Class I (subject to limitations of exemption 21 CFR § 862.9 (b) and (c)(9))
   Class I (reserved)
3. Product code:
   OND
   JJX
4. Panel:
   75 (Clinical Chemistry)

H. Intended Use:

1. Intended use(s):
   See Indications for use.
2. Indication(s) for use:
   The TearLab Osmolarity System is intended to measure the osmolarity of human tears to aid in the diagnosis of patients with signs or symptoms of dry eye disease, in conjunction with other methods of clinical evaluation.

3. Special conditions for use statement(s):
   - For prescription use only.
   - Osmolarity may differ from left and right eye, and each eye should be tested and assessed to determine which eye represents the higher osmolarity.
   - Do not collect tear fluid from a patient within two (2) hours of eye drop use, use of topical medications or lotions on the face or eyes, or removal of eye make-up.
   - Do not collect tear fluid samples from patients wearing makeup on eyelids.
   - Do not collect or store tear samples for transport or testing at a later time.
   - Do not collect tear fluid after ocular surface staining.

- Do not collect tear fluid after invasive ocular diagnostic testing.
- Do not collect tear fluid within 10 minutes after a slit lamp examination.
- Do not collect tear fluid from a patient who has been crying.

4. Special instrument requirements:
   TearLab Osmolarity System

I. Device Description:

The device consists of the following components and accessories: one TearLab Reader, two TearLab Pens, two TearLab Electronic Check Cards, Single Use TearLab Osmolarity Test Cards, and TearLab Control Solutions. The TearLab Osmolarity Test Card, in conjunction with the TearLab Osmolarity System, provides method for determining tear osmolarity using nanoliter (nL) volumes of tear fluid collected directly from the eyelid margin.

To perform a test, a new Test Card containing a microfluidic capillary channel is attached onto the Pen. The tip of the Test Card is touched to the inferior tear meniscus located above the lower eyelid and collects 40-50 nanoliters of tear fluid by passive capillary action. After a successful collection, the Pen in conjunction with the electrodes embedded on the Test Card, measures and stores the tear fluid impedance. The Pen is then docked to the Reader. The Reader downloads impedance data from the Pen in order to calculate and display the final osmolarity as a numerical value displayed in units of mOsms/L.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Wescor, Inc., 5520 Vapro® Vapor Pressure Osmometer (Class I, Exempt)
   Alcon Laboratories, Inc., Schirmer Tear Test (Class I, Exempt)
   Touch Scientific, Inc., Touch Tear IgE Microassay Kit (Class II, k991316)
   Dia-Screen Corp., Diascreen Reagent Strips (Class I, Non-exempt, k971976)
2. Predicate 510(k) number(s):
   k991316, k971976
3. Comparison with predicate:

Similarities				
Item	TearLab Osmolarity System	Wescor 5520 Vapro® Vapor Pressure Osmometer	Alcon Laboratories, Inc., Schirmer Tear Test	Touch Scientific IgE Microassay Kit
Intended Use	Collection and measurement of osmolarity of tears	Measurement of osmolarity of body fluid	Collection and measurement of body tears	Measurement of tear fluid components
Indications For Use	Clinical assessment of	N/A	Clinical assessment of	Clinical assessment

Similarities				
Item	TearLab Osmolarity System	Wescor 5520 Vapro® Vapor Pressure Osmometer	Alcon Laboratories, Inc., Schirmer Tear Test	Touch Scientific IgE Microassay Kit
	tear fluid in Normal and Dry Eye Patients		tear fluid in Normal and Dry Eye Patients	of tear fluid
Detection Method	Quantitative analysis of tear fluid by measurement of osmotic pressure by affect on physicochemical property	Quantitative analysis of body fluid (tears) by measurement of osmotic pressure by affect on physicochemical property	Quantitative analysis of tear fluid	Quantitative analysis of tear fluid
Tear Collection	Collection of tear fluid by passive capillary force	N/A	Collection of tear fluid by passive capillary force	Collection of tear fluid by passive capillary force

Differences				
Item	TearLab Osmolarity System	Wescor 5520 Vapro® Vapor Pressure Osmometer	Alcon Laboratories, Inc., Schirmer Tear Test	Touch Scientific IgE Microassay Kit
Transducti on	Impedance	Vapor Pressure Due Point	N/A	Immunoassay
Collection Material	Plastic	N/A	Filter Paper	N/A
Quantity	Nanoliters	Microliters	Microliters	Microliters

K. Standard/Guidance Document Referenced (if applicable):

- CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition (2004)
- CLSI EP6-A: Evaluation of Linearity of Quantitative Measurement Procedures, A Statistical Approach: Approved Guideline (2003)

L. Test Principle:

The TearLab Osmolarity test utilizes an electrical impedance measurement to provide an indirect assessment of osmolarity. After applying a lot-specific calibration curve, osmolarity is calculated and displayed as a quantitative numerical value.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Contrived tear specimens were distributed across the clinical range of interest, 275–400 mOsms/L, and used for performance testing. Results are summarized below.

Single Instrument Precision

Precisions calculated as defined in CLSI EP5-A2, Evaluation of Precision Performance of Quantitative Measurement Methods. Pairs of contrived tear samples at four osmolarity levels were analyzed. Tear samples were analyzed over 20 consecutive days at two separate times during the day.

Sample	Mean Osmolarity (mOsms/L)	N	Within Run (SD)	Within Run (%CV)	Total (SD)	Total (%CV)
Low	280	80	3.8	1.34	5.2	1.87
Normal	294	80	5.5	1.85	7.3	2.47
Moderate	316	80	4.5	1.41	6.6	2.08
High	345	80	4.5	1.30	8.0	2.33

Between Instrument Precision

5 instruments and 6 replicates each of two samples were tested.

Sample	Mean Osmolarity (mOsms/L)	N	Total (SD)	Total (%CV)
Normal	296	12	4.9	1.64
Moderate	316	12	5.3	1.68

Lot-to-Lot Precision

One site, three lots and four samples were tested.

Sample	Lot 1	Lot 2	Lot 3	Mean Osmolarity (mOsms/L)	N	Total (SD)	Total (%CV)
Low	279	276	277	277	28	3.8	1.39
Normal	295	296	291	294	36	4.9	1.65
Moderate	307	303	301	304	18	6.5	2.15
High	338	326	324	329	36	7.5	2.28

Between Site Precision

Three sites, three instruments, four lots and four samples were tested.

Sample	Mean Osmolarity (mOsms/L)	N	Total (SD)	Total (%CV)
Low	278	170	4.4	1.59
Normal	289	180	6.0	2.09
Moderate	308	180	6.3	2.05
High	336	180	8.8	2.61

b. *Linearity/assay reportable range:*
To establish the linearity of the system through the range of 282-391 mOsms/L, seven samples in a dilution series ranging from 251 – 428 mOsms/L were each run in four replicates on one lot of test cards, one TearLab Reader and two Pens. For the lowest and highest samples tested (251 and 428 mOsms/L respectively), TearLab indicated that the value was either below or above the detectable range. The Pens were randomly assigned. Samples were also run in duplicate on the Wescor 5520 Vapor Pressure Osmometer. Results are summarized below:

Regression	Intercept	r^2
0.928	15.976	0.9903

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
OcuSense TearLab Control Solutions are two levels of aqueous salt solution sealed within glass ampoules. These solutions are formulated gravimetrically at two different sodium concentrations. Product stability is established based on real time studies. Samples were analyzed at predetermined intervals with failure defined as greater than a 2% change in sodium concentration.

Closed Vial Stability of Control Solution: control solutions contained within sealed glass ampoules were evaluated at two temperatures, 2-8 °C and 30 °C. The sodium concentration was determined using a flame photometer analyzer (n=5). The mean and percent change was calculated after 36 months after the date of manufacture. The sponsor determined that the control solutions contained within a single use glass ampoule is stable for 36 months when stored at 2-30°C.

The TearLab Osmolarity Systems are calibrated against a set of precision resistors and temperature references. This procedure has been established to ensure that all TearLabs operate within identical tolerance limits.

d. *Detection limit:*
The upper and lower limit of detection of the TearLab Osmolarity System is 275-400 based on replicates of two levels of contrived tears, at 275 mOsms/L (7 replicates) and 400 mOsms/L (21 replicates), respectively, tested on one lot of test cards with one TearLab Reader and one Pen. Paired with the linearity testing performed above in section L.b., the sponsor has demonstrated that the device is capable of reading values as low as 275 mOsms/L and as high as 400 mOsms/L with linearity established from 282-391 mOsms/L.

e. *Analytical specificity:*
To establish the effects of matrix components on the osmolarity of human tears, sodium chloride solutions were compared to a complex mixture of mono- and divalent ions formulated to mimic human tears. Both matrices were analyzed on a Wescor 5520 Vapro vapor pressure osmometer calibrated using a 290 mmol/kg NIST traceable NaCl solution. The fluid samples were also measured for impedance on a TearLab device.

Linear regression analysis showed that the difference between sodium chloride solution and a complex mixture of mono- and divalent ions meant to mimic human tears was approximately 750 Ohms across a range of osmolarities, representing a shift of 8 mOsms/L. Because physiological variance in electrolyte ratios is expected to be less than 1-10% of each electrolyte, the expected change in osmolarity resulting from these variations is 0.08 to 0.8 mOsms/L. As this range is not clinically relevant, the sponsor concludes that there are no measurable matrix effects from the physiological variance in electrolyte composition in human tears.

Linear regression analysis showed that the difference between artificial tears comprised of of monovalent ions, divalent ions, and tear proteins (specifically, lysozyme, immunoglobulins and albumin), as compared to the same matrix without tear proteins, was less than the measurable precision of the TearLab (< 3 mOsms/L). Because physiological variance in protein ratios is expected to be much less than the 100% difference within this experiment, there are no expected matrix effects from physiological variance in protein composition in human tear.

Linear regression analysis showed that the difference between artificial tears comprised of of monovalent ions, divalent ions, tear proteins, lipids and mucins as compared to the same matrix without lipids and mucins, was less than the measurable precision of the TearLab (< 3 mOsms/L). Because physiological variance in protein ratios is expected to be much less than the 100% difference within this experiment, there are no expected matrix effects from physiological variance in lipid and mucin composition in human tear.

Therefore, there are no expected matrix effects from physiological variance in electrolyte composition, protein composition, or lipid and mucin composition in human tears.

f. Assay cut-off:
Not Applicable.

2. Comparison studies:

a. Method comparison with predicate device:
Seven levels of contrived tear solution were prepared and distributed throughout the clinically significant range of osmolarity for a total of 80 samples ranging from 280 to 372 mOsms/L and measured on the predicate Wescor 5520 Vapro Osmometer and the TearLab Osmolarity System. The Deming regression between the individual Wescor values (x) and individual Tearlab values (y) is shown below.

Parameter	Coefficient	Std Error	95% CI
Intercept	23.061	8.470	6.201 to 39.920
Slope	0.9146	0.0276	0.8597 to 0.9694
Correlation coefficient (r^2)	0.9588		
Regression Equation	y = 0.9146x + 23.061		

At each of three physician office sites, forty contrived tear specimens across seven levels of the clinically significant range ranging from from 280 to 372 mOsms/L were prepared and measured on the TearLab Osmolarity System. The physician office laboratories did not have access to the Wescor 5520 Vapro vapor pressure osmometer. Wescor values were determined by an average of 2-3 measurements on each level of osmolarity immediately prior to the beginning of the study by the sponsor.

Number of sites	N	Regression	r^2
3	120	y = 0.9402x + 12.512	0.9515

b. Matrix comparison:
Not applicable. Tears are the only indicated matrix.

3. Clinical studies:
   a. Clinical Sensitivity:
   Not Applicable.
   b. Clinical specificity:
   Not Applicable.
   c. Other clinical supportive data (when a. and b. are not applicable):
   Calibration Data – Determination of the Cutoff
   To determine clinical performance for tear film hyperosmolarity in the diagnosis of Dry Eye Disease (DED) a meta-analysis was performed[1] on historical published data for tear osmolarity in samples of normal and dry eye subjects. An osmolarity referent 316 mOsms/L was found to yield sensitivity of 69%, specificity of 92%, and an overall predictive accuracy of 82% for the diagnosis of dry eye syndrome.

Performance of Osmolarity in meta-analysis

	Normal	Dry Eye	Total	
≤ 316	750	192	942	80% NPV
> 316	65	429	494	87% PPV
Total	815	621	1436	
	Specificity	Sensitivity	Accuracy	
	92%	69%	82%	

[1]Tomlinson A, Khanal S, Ramaesh K, Diaper C, McFadyen A. Tear Film Osmolality: Determination of a Referent for Dry Eye Diagnosis," Investigative Ophthalmology & Visual Science, October 2006; 47(10) 4309-4315

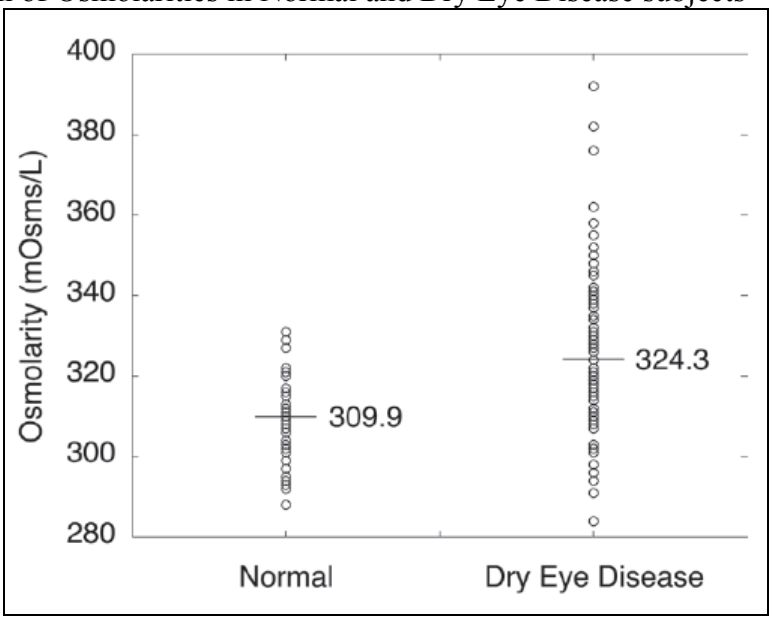
Performance on patients with objective signs of dry eye – Validation of Cutoff
140 subjects were enrolled in a multicenter study (n = 45 Normal, n = 95 Dry Eye). To qualify as a Dry Eye patient, subjects were required a positive score on the Ocular Surface Disease Index (OSDI) and 2 or more positive indications of Tear Film Breakup Time (TBUT), Schirmer Test, Corneal Staining, Conjunctival Staining, or Meibomian Gland Dysfunction. Performance of the TearLab™ Osmolarity System

using these selection criteria are shown below in Table 2 below.

TearLab Osmolarity Diagnostic Performance for Dry Eye Disease

	Normal	Dry Eye	Total	
≤ 316	32	34	66	48% NPV
> 316	13	61	74	82% PPV
Total	45	95	140	
	Specificity	Sensitivity		
	71%	64%		

Distribution of Osmolarities in Normal and Dry Eye Disease subjects



In the study detailed above, each of the signs showed the following performance:

Diagnostic performance of TearLab Osmolarity Compared to other Clinical Signs

Sign	Specificity	Sensitivity	NPV	PPV
TearLab Osmolarity	71%	64%	48%	82%
TBUT	46%	77%	41%	80%
Corneal Staining	68%	65%	42%	85%
Conjunctival Staining	41%	82%	49%	77%
Meibomian Dysfunction	68%	61%	41%	83%

4. Clinical cut-off**:**
   Not Applicable.

5. Expected values/Reference range:
   The sponsor gives the following as the reference tear osmolarity values for normal and dry eye disease patients based on the validation of cutoff study found above in section 3.c.:
   Normal: 288-331 mOsms/L (90% CI 288-331, mean 309.9 ± 11.0)
   Dry Eye Disease: 291-382 mOsms/L (90% CI 284-392, mean 324 ± 20.8)

N. Instrument Name:

TearLab Osmolarity System

O. System Descriptions:

1. Modes of Operation:
   Each test card is single use and must be replaced with a new card for additional readings.
2. Software:
   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:
   Yes ___X____ or No _____
3. Specimen Identification:
   There is no sample identification function with this device. Samples are applied directly to the test strip as they are collected.
4. Specimen Sampling and Handling:
   This device is intended to be used with tears from the lateral (temporal) extent of the eyelid. Since the tear sample is applied directly to the test strip there are no special handling or storage issues.
5. Calibration:
   The manufacturer calibrates the TearLab Osmolarity System against a reference standard solution prepared from dried, high-purity sodium chloride traceable to the National Institute of Standards and Technology (NIST). Calibration by the user is not required.
6. Quality Control:
   The sponsor has two levels of controls available for this device with both normal and high osmolarity control solutions available in single-use glass ampoules. An acceptable range for each control level is printed on control package insert. The user is instructed to not use the device if the control solutions are outside of the range indicated and to contact the distributor.

   The Electronic Check Cards (ECC) will also verify TearLab function. The Electronic Check Card contains precision resistors on a printed circuit board to provide a known standard signal to simulate tear impedance. The user attaches the ECC to the Pen, which converts the precision resistor signal of the ECC into an osmolarity test result that should be compared to the allowable range as indicated in the ECC instructions for use. In this manner, the user can verify that the Pen and Reader hardware and software are performing as expected.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Rationale For Contrived Tears

To perform the within-run, between instrument, lot-to-lot, and method comparison studies presented in this submission, approximately one half liter of tear fluid would be necessary which is equivalent of fifty thousand tear collections. Comparison of sequential tear collections on the predicate Wescor and TearLab osmometer are also made impractical by the small volume of accessible human tear fluid per subject. Additionally, split sample in vitro tests of tear fluid were found by the sponsor to be unsuitable for the external clinical sites enrolled to examine the performance of the TearLab.

In order to mitigate errors due to evaporation or dilution from reflex tearing during performance testing of the TearLab, the sponsor synthesized artificial tears that accurately represented the impedance-osmolarity relationship of human tear fluid. To demonstrate the acceptability of using contrived tears in place of human tears, roughly one half liter of contrived tear solution was synthesized under an ISO 13485 quality system in an independent reference laboratory. The composition of the contrived tear contained a complex mixture of mono- and divalent ions, proteins, lipids and metabolites to mimic the human tear matrix. The contrived tears were then diluted to produce seven osmolarity specimens representing the clinical range of tear osmolarity (280, 287, 294, 305, 316, 345, 372 mOsms/L). Samples were analyzed on a Wescor 5520 osmometer calibrated using a 290 mmol/kg NIST traceable NaCl solution and an OcuSense TearLab device. The contrived tear solution was split into 0.4 mL aliquots in individually sealed vials that were then disseminated to the performance testing sites.

In addition, to demonstrate the performance of human tear fluid measurement with the Tearlab osmometer, a pool of human tears was collected from 43 different people, of which a portion was split into four fractions and partially lyophilized to increasing levels of osmolarity. The fractions were then measured on both the TearLab and Wescor 5520 osmometers.

Wescor Osmolarity vs. TearLab Osmolarity

Test	Slope	Intercept	r^2
Human Tears	0.9626	10.964	0.9531
Contrived Tears	0.9455	12.433	0.95

The impedance-osmolarity relationship of the contrived tears used for performance testing was identical to that of human tears.

Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

R. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.