K090901

510(k) SUMMARY: eSensor® CF Genotyping Test on XT-8 System

Preparation Date: June 12, 2009

Submitted By:
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JUL - 6 2009

Contacts:
Robert Dicheck, Vice President - Quality & Regulatory Affairs (Official Correspondent)
Aviva Jacobs, Ph.D., Associate Director - Product Development (Project Manager)

Proprietary Names and Classifications:

For the assay:
eSensor® CF Genotyping Test (Kit)
Regulation: 21CFR 866.5900
Panel: Immunology (82)
Classification: II
Product Code: NUA - Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Gene Mutation Detection System

For the instrument:
eSensor® XT-8 Instrument (System)
Regulation: 21CFR 862.2570
Panel: Clinical Chemistry (75)
Classification: II
Product Code: NSU - Instrument for Clinical Multiplex Test Systems

Common name:
Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Gene Mutation Detection System

Intended uses:
The eSensor® CF Genotyping Test is an *in vitro* diagnostic device used to simultaneously detect and identify a panel of mutations and variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in genomic DNA samples isolated from human peripheral whole blood specimens. The panel includes mutations and variants recommended by the 2004 American College of Medical Genetics (ACMG). The eSensor® CF Genotyping Test is a qualitative genotyping test that provides information intended to be used for cystic fibrosis carrier screening as recommended by ACMG and the 2005 American College of Obstetricians and Gynecologists (ACOG) for adults of reproductive age, as an aid in newborn screening for cystic fibrosis, and in confirmatory diagnostic testing for cystic fibrosis in newborns and children. The test is not indicated for use in fetal diagnostic or pre-implantation testing. This test is also not indicated for stand-alone diagnostic purposes and results should be used in conjunction with other available laboratory and clinical information.

Special conditions for use statement(s):
For Prescription Use Only

The eSensor® CF Genotyping Test is an *in vitro* diagnostic device intended for genotyping multiple mutations or polymorphisms in an amplified DNA sample utilizing electrochemical detection technology, for use on the eSensor® XT-8 Instrument.

Predicate devices:
eSensor® CFCD System, K060543 and K051435
InPlex™ CF Molecular Test, K063787
eSensor® XT-8 Instrument, K073720

Device Description:
The eSensor® CF Genotyping Test on the eSensor® XT-8 System is an *in vitro* diagnostic device for performing hybridization and genotyping of multiple mutations and/or polymorphisms in an amplified DNA sample. A single-use, disposable test cartridge is used to perform hybridization and genotyping. The cartridge contains an EEPROM chip which transmits the cartridge lot number, expiration date and protocol identity to the XT-8 instrument.

The analysis process for each sample consists of three steps: 1) Genomic DNA isolated from whole blood obtained using EDTA as anti-coagulant is combined with PCR Mix and Taq polymerase enzyme and is subjected to amplification of target sequences by PCR using a thermal cycler. 2) Amplified DNA is treated with exonuclease enzyme to generate single-stranded target DNA. 3) Single-stranded, amplified target DNA is mixed with hybridization and genotyping reagents and transferred to an eSensor® CF Genotyping Tet cartridge, and the cartridge is inserted in the eSensor® XT-8 Instrument. The instrument controls the circulation of the sample inside the cartridge to allow hybridization at a controlled temperature and then detects and genotypes the sample by voltammetry.

Genotyping of the test panel polymorphisms is achieved by a sandwich assay principle: 1) Each pair of electrodes contains a different synthetic oligonucleotide capture probe which is complementary to one of the target DNA fragments. 2) The hybridization reagents contain pairs of ferrocene-labeled synthetic oligonucleotide signal probes; one member of each pair is complementary to the major allele sequence of the target polymorphism, while the second member of the pair is complementary to the minor allele sequence. Each member of the probe pair has a ferrocene label with a different oxidation potential for each allele. 3) Single-stranded, amplified target DNA hybridizes to its specific capture probe, and in turn hybridizes to the allele-specific, ferrocene-labeled signal probe. 4) Each electrode of the array is analyzed by voltammetry; the target polymorphism is determined by the location of the electrode containing the capture probe, and the genotype is identified by the ratio of signals from the allele-specific ferrocene labels. The array also includes positive and negative controls to confirm the hybridization reaction and detect non-specific signals.

Upon completion of the test, the EEPROM chip on the cartridge contains information that prevents its re-use with a new sample. The eSensor® XT-8 instrument analyzes the results and provides a report of the test results.

Comparison to technological features of the predicate devices:
The following is a comparison of the Osmetech Molecular Diagnostics eSensor® CF Genotyping Test on the XT-8 System to the predicates.

Characteristic	eSensor® CFCD System (Predicate 1: K060543 and K051435)	InPlex™ CF Molecular Test (Predicate 2: K063787)	eSensor® CF Genotyping Test
Test type	Qualitative genetic test for single nucleotide polymorphism detection	Qualitative genetic test for single nucleotide polymorphism detection	Same as predicates 1 and 2
Sample Type	Genomic DNA obtained from a human whole blood sample	Genomic DNA obtained from a human whole blood sample	Same as predicates 1 and 2
Target of detection	Single-nucleotide polymorphism	Single-nucleotide polymorphism	Same as predicates 1 and 2
DNA extraction	Performed off-line	Performed off-line	Same as predicates 1 and 2
Genes	CFTR	CFTR	Same as predicates 1 and 2
Number of Loci genotyped	23 mutations and 1 variant as recommended by ACMG (2004)/ACOG (2005).	23 mutations and 4 variants recommended by ACMG (2004)/ACOG (2005).	Same as predicates 1
Genotyping reaction location	Test cartridge	Microfluidic card	Same as predicate 1
Genotyping principle	Sandwich hybridization test	Fluorometric resonance energy transfer (FRET)	Same as predicate 1
Instrument operating system	eSensor® Instrument Model 4800	Multi-well fluorometer	eSensor® Instrument Model XT-8 Random access compatible with multiple simultaneous test types.
Assay results	Assay signal results are interpreted by a software program and are assigned result that is presented to the end-user in a report format	InPlex™ CF Molecular Test Call Reporting Software	Assay signal results are interpreted by a software program and are assigned a result that is presented to the end-user in a report format

Performance Characteristics:

Site to Site, Operator to Operator, Day to Day, Run to Run and sample to sample reproducibility

A reproducibility study was performed over 5 non consecutive days at 3 different sites (2 external sites and 1 internal site). Each site performed the testing twice each day, using two different operators and the same testing materials. Twenty two (22) gDNA samples containing positive calls for all ACOG/ACMG panel mutations in addition to the 5/7/9T polymorphism were used. For practical considerations, the 22 samples were divided into 2 set of 11 samples, so that the sample set was run in duplicate to evaluated intra assay reproducibility using a single kit. Only one lot of materials was used for this study.

Summary of Inter-laboratory, Inter-operator, Reproducibility Results

By Site	By Operator	Number of Sample Replicates	First-pass Correct calls	First-pass No-calls	First-pass Miscalls	Final Correct calls	Final incorrect calls	% Agreement
Site A (Internal)	Operator 1	220	208	12	0	220	0	100%
	Operator 2	220	216	4	0	220	0	100%
Site B: (External)	Operator 1	220	215	5	0	220	0	100%
	Operator 2	220	211	9	0	220	0	100%
Site C (External)	Operator 1	220	216	4	0	220	0	100%
	Operator 2	220	218	2	0	220	0	100%
	Total	1320	1284	36	0	1320	0	100%

Summary of Reproducibility Results by Sample Genotype and Site

Sample Genotype by Sequencing	5/7/9T	Number of Sample Replicates tested by eSensor® CF Genotyping Test			Number of CF Sample Calls Before Repeat Testing					Number of CF Sample Calls After Repeat Testing			
		Site A	Site B	Site C	Site A Correct Calls	Site B Correct Calls	Site C Correct Calls	No Calls	Miscalls	Site A Correct calls	Site B Correct Calls	Site C Correct calls	No Calls
1717-1G>A	7T/7T	60	60	60	59	59	59	3	0	60	60	60	0
1898+1G>A/ΔF508	7T/9T	60	60	60	59	60	58	3	0	60	60	60	0
2184delA/ΔF508	7T/9T	60	60	60	58	60	58	4	0	60	60	60	0
3120+1G>A/621+1G>T	7T/9T	60	60	60	59	60	59	2	0	60	60	60	0
2789+5G>A/2789+5G>A	7T/7T	60	60	60	59	60	59	2	0	60	60	60	0
3659delC/ΔF508	7T/9T	60	60	60	59	59	60	2	0	60	60	60	0
3849+10KbC>T/ΔF508	7T/9T	60	60	60	60	59	58	3	0	60	60	60	0
621+1G>T/G85E	7T/9T	60	60	60	58	60	60	2	0	60	60	60	0
711+1G>T/621+1G>T	7T/9T	60	60	60	59	60	60	1	0	60	60	60	0
A455E/621+1G>T	9T/9T	60	60	60	59	60	59	2	0	60	60	60	0
ΔI507	7T/7T	60	60	60	60	60	60	0	0	60	60	60	0
G542X	7T/9T	60	60	60	59	59	60	2	0	60	60	60	0
G551D/R347P	7T/7T	60	60	60	59	59	60	2	0	60	60	60	0
N1303K	7T/9T	60	60	60	60	60	60	0	0	60	60	60	0
R1162X	7T/7T	60	60	60	60	60	59	1	0	60	60	60	0
R117H/ΔF508	5T/9T	60	60	60	60	60	59	1	0	60	60	60	0
R334W	7T/7T	60	60	60	60	59	59	2	0	60	60	60	0
R553X/G551D	7T/7T	60	60	60	59	60	60	1	0	60	60	60	0
R560T/ΔF508	7T/9T	60	60	60	59	60	60	1	0	60	60	60	0
W1282X	5T/7T	60	60	60	59	60	59	2	0	60	60	60	0
WT	7T/7T	60	60	60	60	60	60	0	0	60	60	60	0
R117H/ΔF508	5T/9T	60	60	60	60	60	60	0	0	60	60	60	0

Lot to Lot Reproducibility

A total of 21 genomic DNA samples covering all possible genotypes were tested using three different kit lots and tested using the eSensor® CF Genotyping Test. The data were evaluated after first-pass results and following additional runs for no-calls. All samples gave 100% correct calls when compared with DNA sequencing. No impact of kit lot observed in this study. The following table summarizes the results of lot to lot reproducibility study.

LOT	Samples Tested	First pass correct calls	First pass		Final		Final correct calls	% Agreement
			No Calls	Miscalls	No Calls	Miscalls		
1	21	21	0	0	0	0	21	100%
2	21	21	0	0	0	0	21	100%
3	21	20	1	0	0	0	21	100%
Total	63	62	1	0	0	0	63	100%

Genomic DNA Extraction Reproducibility

A total of 20 whole blood samples of different genotypes were extracted by three commonly used extraction methods and tested using the eSensor® CF Genotyping Test.. The data were evaluated after first-pass results and following additional runs for no-calls. All samples gave 100 correct calls when compared with DNA sequencing. There was no impact of extraction method observed in this study. The following table summarizes the results of extraction reproducibility study.

Extraction Method	# Samples Tested/Genotype	First pass correct calls	First pass No Calls	Miscalls	Final correct calls	Final Agreement
A	20	17	3	0	20	100
B	20	18	2	0	20	100
C	20	19	1	0	20	100

Method Comparison

In a method comparison study, a total of 112 gDNA samples extracted from whole blood with A260-280 ratios of 1.2-2.5 were genotyped using the eSensor® CF Genotyping Test and DNA sequencing.

All samples gave 100% agreement with DNA sequencing. The following table summarizes the results of the method comparison study.

Genotype by sequencing	Calls per mutation	Sequencing Calls		1st Pass CF GT Calls			% Agreement			FINAL CF GT Calls			% Agreement		
		Pos	Neg	Pos	Neg	No Calls	Overall	Pos	Neg	Pos	Neg	No Calls	Overall	Pos	Neg
ΔF508	112	47	65	46	65	1	99.1	97.9	100	47	65	0	100	100	100
G542X	112	7	105	6	105	1	99.1	85.7	100	7	105	0	100	100	100
W1282X	112	6	106	6	106	0	100	100	100	6	106	0	100	100	100
G551D	112	8	104	8	104	0	100	100	100	8	104	0	100	100	100
621+1G>T	112	7	105	7	105	0	100	100	100	7	105	0	100	100	100
N1303K	112	8	104	7	104	1	99.1	87.5	100	8	104	0	100	100	100
R553X	112	4	108	4	108	0	100	100	100	4	108	0	100	100	100
ΔI507	112	3	109	3	109	0	100	100	100	3	109	0	100	100	100
3120+1G>A	112	2	110	2	110	0	100	100	100	2	110	0	100	100	100
3849+10kbC>T	112	5	107	5	107	0	100	100	100	5	107	0	100	100	100
R117H	112	8	104	8	104	0	100	100	100	8	104	0	100	100	100
1717-1G>A	112	5	107	5	107	0	100	100	100	5	107	0	100	100	100
2789+5G>A	112	5	107	5	107	0	100	100	100	5	107	0	100	100	100
R334W	112	4	108	4	108	0	100	100	100	4	108	0	100	100	100
R347P	112	4	108	4	108	0	100	100	100	4	108	0	100	100	100
711+1G>T	112	4	108	4	108	0	100	100	100	4	108	0	100	100	100
R560T	112	4	108	3	108	1	99.1	75.0	100	4	108	0	100	100	100
R1162X	112	8	104	8	104	0	100	100	100	8	104	0	100	100	100
3659delC	112	4	108	4	108	0	100	100	100	4	108	0	100	100	100
A455E	112	2	110	2	110	0	100	100	100	2	110	0	100	100	100
G85E	112	7	105	7	105	0	100	100	100	7	105	0	100	100	100
2184delA	112	2	110	2	110	0	100	100	100	2	110	0	100	100	100
1898+1G>A	112	2	110	2	110	0	100	100	100	2	110	0	100	100	100
Reflex Polymorphism															
IVS8--8 5T/7T/9T Variant (§)	112	6 ‡	106	6 ‡	106	0	100	100	100	6	106	0	100	100	100
Polymorphisms not specifically genotyped															
I507V	112	1	111	1	111	0	100	100	100	1	111	0	100	100	100
F508C	112	1	111	1	111	0	100	100	100	1	111	0	100	100	100
Potentially interfering mutations not part of assay panel															
2183AA>G	112	2	110	2	110	0	100	100	100	2	110	0	100	100	100
R117L	112	1	111	1	111	0	100	100	100	1	111	0	100	100	100
Grand Total	**2688**	**162**	**2526**	**158**	**2526**	**4**	**99.9**	**97.5**	**100**	**162**	**2526**	**0**	**100**	**100**	**100**

§ For the purpose of the IVS8-5T/7T/9T Variant, "Positive" samples are regarded as those that have at least one copy of the 5T allele while "Negative" samples are regarded as having only the 7T and/or 9T allele. ‡1 sample is 5T/5T Mutant.
The number of positive sequencing calls is greater than the number of independent samples due to the inclusion of compound heterozygous samples.
The Grand Total consists of the total number of sequencing calls for mutations, the 1 5T/5T sample included, polymorphisms not specifically genotyped, and the potentially interfering mutations not part of assay panel. I507V, F508C, 2183AA>G, and R117L are non-panel polymorphism containing samples correctly called as Wild-Type, which are not included in the grand total for calls. No samples with I506V were tested.

Other Characteristics of the eSensor® CF Genotyping Test:

Characteristic	Result
Limit of detection	Two genomic DNA samples of different genotypes were extracted from whole blood stored in EDTA and serially diluted and tested 20 times each at input amounts of 0.01, 0.1, 1, 10, 100, 500 and 1000 ng/PCR. using the eSensor® CF Genotyping Test. An additional run was performed for tests that gave a first pass no call result.. All input amounts from 0.01ng to 1000ng for both samples gave equivalent final performance. (100% Agreement with 98.76%, 95% LCB), (99.95% LCB on a per SNP basis). The limit of detection was established as the lowest concentration at which no-calls or mis-calls were obtained. The lower detection limit was determined to be 0.1 ng of purified DNA per reaction and the upper detection limit was determined to be 1000 ng of purified DNA per reaction. The recommended range of DNA input amounts for the eSensor® CF Genotyping Test is from 10 to 500 ng.
Interfering substances	Test performance was not affected by addition of the following substances seven whole blood samples of different genotypes prior to extraction: • Bilurubin (30 mg /dL whole blood). • Triglycerides (500 mg/dL whole blood). • Hemoglobin (~20g /dL whole blood). • EDTA (at a concentration equivalent to 5-fold higher than that provided by a standard EDTA blood collection tube)
Test Limitations	The eSensor® CF Genotyping Test does not identify all possible mutations in the CFTR gene, for example E60X, I148T, 1078delT, V520F, 2143delT, 3199del6, D1152H, 3876delA, 2183AA>G, R560K, R117L, R347H, G551S, 711+5G>A, 394delTT,and 3905insT. A negative result for all the mutations in this panel does not necessarily indicate that the individual is negative for cystic fibrosis (carrier or affected status). The mutations included in this test represent >80% of the mutations carried by Caucasian American adults. The eSensor® CF Genotyping Test does not identify the I506V, I507V, and F508C polymorphisms, thus in the case of ΔF508 homozygosity, reflex testing by bi-directional DNA sequencing is recommended
Interfering mutations and polymorphisms	More than 1,000 mutations have been identified in the CFTR gene with varying confidence that they are CF disease causing. When present in the same region as a panel mutation, they may interfere with genotyping results The following mutations have been evaluated and demonstrated not to impact the results of the eSensor® CF Genotyping Test

Non-Panel Mutation or Polymorphism	ACOG/ACMG Panel Mutation
2183AA>G	2184delA
R117L	R117H

Kit Stability:
eSensor® CF Genotyping Test kit components should be stored under the appropriate conditions until the expiration date printed on the label:

- PCR Box containing CF Genotyping Test PCR Mix and Taq Polymerase: Store at -20°C in a designated pre-PCR area.
- Cartridges: Store at 10° to 25°C
- Genotyping Box containing Exonuclease, CF Genotyping Test Signal Buffer, XT-Buffer 1 and XT-Buffer 2: Store at -20°C in a designated post-PCR area.

In-process stability has been established for the following components, working reagents and samples:

- Cartridges can be stored for up to 14 days after opening the foil pouches. If stored, cartridges should be kept in their original foil pouch at room temperature in a dry place with the zip-loc closure sealed.
- Once open, reagents can be stored at -20°C for up to 30 days.
- Reagents can be thawed up to 3 times.
- Whole blood stored in EDTA can be stored for up to 4 weeks after collection prior to extraction of gDNA for use in the eSensor® CF Genotyping Test.
- PCR product can be stored at 4°C or -20°C for up to 7 days.
- Exonuclease-digested PCR product can be stored store at 4°C or -20°C for up to 7 days.
- After combining the exonuclease-digested PCR with hybridization reagents, the hybridization reaction can be loaded on the cartridge and held at ambient temperature for up to 8 hours before initiating hybridization of the cartridge on the XT-8 instrument.

Conclusion:
The above internal and clinical test results support the safety and effectiveness of the eSensor® CF Genotyping Test on the eSensor® XT-8 System, and demonstrate substantial equivalence to the predicate device.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Building 66
Silver Spring, MD 20993

Osmetech Molecular Diagnostics
c/o Mr. Robert S. Dicheck,
Vice President - Quality & Regulatory Affairs
757 S. Raymond Avenue
Pasadena, CA 91105

JUL - 6 2009

Re: k090901
Trade/Device Name: eSensor® CF Genotyping Test
Regulation Number: 21 CFR 866.5900
Regulation Name: CFTR (cystic fibrosis transmembrane conductance regulator) gene mutation detection system
Regulatory Class: Class II
Product Code: NUA, NSU
Dated: June 9, 2009
Received: June 10, 2009

Dear Mr. Dicheck:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter

will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5451. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Maria M. Chan, Ph.D.
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

Indication(s) for Use

510(k) Number (if known): k090901

Device Name: eSensor® CF Genotyping Test

Intended Use/Indication(s) For Use:

The eSensor® CF Genotyping Test is an in vitro diagnostic device used to simultaneously detect and identify a panel of mutations and variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in genomic DNA samples isolated from human peripheral whole blood specimens. The panel includes mutations and variants recommended by the 2004 American College of Medical Genetics (ACMG). The eSensor® CF Genotyping Test is a qualitative genotyping test that provides information intended to be used for cystic fibrosis carrier screening as recommended by ACMG and the 2005 American College of Obstetricians and Gynecologists (ACOG) for adults of reproductive age, as an aid in newborn screening for cystic fibrosis, and in confirmatory diagnostic testing for cystic fibrosis in newborns and children. The test is not indicated for use in fetal diagnostic or pre-implantation testing. This test is also not indicated for stand-alone diagnostic purposes and results should be used in conjunction with other available laboratory and clinical information.

The eSensor® CF Genotyping Test is intended for use on the eSensor® XT-8 System.

Prescription Use __X__ (21 CFR Part 801 Subpart D) And/Or Over the Counter Use ____. (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) k090901