JUL 09 2010

510(k) number: **K100818** **Date of preparation:** June 21, 2010

Submitter: **Meridian Bioscience, Inc.**
Submitter's address: 3471 River Hills Drive
Cincinnati, Ohio 45244
Contact: Michelle Smith
Contact number: (513) 271-3700

Device name: ***illumigene*™ *C. difficile***
***illumipro-10*™ Automated Isothermal Amplification and Detection System**
***illumigene*™ *C. difficile* External Control Kit**

Common name: *C. difficile* DNA Amplification Assay
Classification name: *C. difficile* Nucleic Acids
OMN, CFR Section 866.2660

Predicate device: K091109: Cepheid® Xpert® *C. difficile*
Model GXVDIFFICILE-10,900-0423, 900-0065, 900-0144, 900-0145, 900-0146, 900-0381, 900-0391, 900-0392, 900-393, 950-0151

Reference comparator: Cytotoxic bacterial culture

Description of the device:

The ***illumigene*** Molecular Diagnostic Test System is comprised of the ***illumigene C. difficile*** DNA Amplification Test Kit, the ***illumigene C. difficile*** External Control Kit and the *illumipro-10* Automated Isothermal Amplification and Detection System. The ***illumigene C. difficile*** DNA amplification assay utilizes loop-mediated isothermal amplification (LAMP) technology to detect the presence of toxigenic *C. difficile* in patients suspected of having *C. difficile* associated disease (CDAD). Each ***illumigene C. difficile*** assay is completed using an ***illumigene*** Sample Preparation Apparatus, ***illumigene*** Reaction Buffer, ***illumigene C. difficile*** Test Device, Sample Collection Brush, and ***illumigene*** Extraction Tube. Samples are prepared using the Sample Collection Brush and the ***illumigene*** Sample Collection Apparatus, target DNA is heat extracted in the Extraction Tube and DNA amplification occurs in the ***illumigene C. difficile*** Test Device.

The ***illumipro-10*** heats each ***illumigene C. difficile*** Test Device containing prepared samples, facilitating amplification of target DNA. When toxigenic *C. difficile* is present in the patient sample, a cytotoxin specific sequence is amplified and Magnesium pyrophosphate is formed. Magnesium pyrophosphate forms a precipitate in the reaction mixture. The ***illumipro-10*** detects the change in light transmission through the reaction mixture created by the precipitating Magnesium pyrophosphate. Sample results are reported as Positive or Negative based on the detected change in transmission.

The ***illumigene C. difficile*** External Control Kit consists of a Positive Control Reagent and a Negative Control Reagent. External Control reagents are provided to aid the user in detection of reagent deterioration, adverse environmental or test conditions, or variance in operator performance that may lead to test errors. The ***illumigene C. difficile*** External Control Kit is required for routine Quality Control.

Meridian Bioscience, Inc.	510(k) Application *illumigene C. difficile*	
	Description:	**510(k) Summary *illumigene C. difficile***
	Identification:	Attachment 003. Revision 002
	Date:	June 21, 2010

Intended Use:

The ***illumigene*** *C. difficile* DNA amplification assay, performed on the ***illumipro-10,*** is a qualitative *in vitro* diagnostic test for the direct detection of toxigenic *C. difficile* in human stool specimens from patients suspected of having *Clostridium difficile*-associated disease (CDAD).

The ***illumigene*** *C. difficile* assay utilizes loop-mediated isothermal DNA amplification (LAMP) technology to detect the pathogenicity locus (PaLoc) of toxigenic *Clostridium difficile*. The *Clostridium difficile* PaLoc is a gene segment present in all known toxigenic *C. difficile* strains. The *C. difficile* PaLoc codes for both the Toxin A gene (*tcdA*) and the Toxin B gene (*tcdB*), has conserved border regions, and is found at the same site on the *C. difficile* genome for all toxigenic strains[3]. The ***illumigene*** *C. difficile* assay detects the PaLoc by targeting a partial DNA fragment on the Toxin A gene. The *tcdA* target region was selected as an intact region remaining in all known A+B+ and A-B+ toxinotypes.

illumigene *C. difficile* is intended for use in hospital, reference or state laboratory settings. The device is not intended for point-of-care use.

Comparison to predicated device:

Characteristic	*Illumigene*™ C. *difficile*	Cepheid® Xpert® *C. difficile*
Test Format	DNA Amplification Assay	DNA Amplification Assay
Intended Use		
DNA Amplification Technology	Loop-Mediated Isothermal Amplification (LAMP)	Real-Time Polymerase Chain Reaction (PCR)
Target Sequences Detected	Partial DNA fragment on the Toxin A gene of the pathogenicity locus (PaLoc) found in all known strains for toxigenic *C. difficile*.	Toxin B sequences
Qualitative/Quantitative	Qualitative	Qualitative
Screening, Diagnostic or Identification Test	Diagnostic	Diagnostic
Specimen Types		
Unformed Human Stool	Yes	Yes
Human Stool in Cary-Blair-based Media	Yes	No
Reagents/Components	***illumigene*** Sample Preparation Apparatus ***illumigene*** Reaction Buffer ***illumigene*** *C. difficile* Assay Device ***illumigene*** Extraction Tubes Sample Collection Brushes	Xpert *C. difficile* Assay cartridges Sample Reagent Reagent 1 Reagent 2
Extraction	Manual	Self-contained and automated
Amplification	Self-contained and automated	Self-contained and automated
Detection	Self-contained and automated	Self-contained and automated
Testing Time	Approximately 60 minutes	Approximately 45 minutes

Calibration	Not required	Not required

Comparison to predicated device:

Characteristic	***Illumigene*™ C. *difficile***	**Cepheid® Xpert® *C. difficile***
Controls		
Inhibition, Assay	Provided ***illumigene*** Sample Preparation Apparatus: *Staphylococcus aureus* ***illumigene C. difficile*** Assay Device: *Staphylococcus aureus* LAMP Primers	Provided Sample Processing Control (SPC): *Bacillus globigii* Probe Check Control (PCC): Fluorescence emitting probes
External	Adjunct Reagents ***illumigene C. difficile*** External Control Kit Catalog 279920	User Supplied KWIK-STIK™ from MicroBioLogics catalog 0329 (toxigenic C. *difficile*) as positive control KWIK-STIK™ from MicroBioLogics catalog 0331 (*C. sordelli*) as negative control
Extraction	User Supplied	User Supplied
Equipment		
Instrumentation	***illumipro-10***™ Automated Isothermal Amplification and Detection System	GeneXpert® Dx System
General Laboratory Equipment	Micropipette 50 µL, 200 µL Dry-bath with 12mm heat block, 95 C Interval Timer Vortex Mixer	Vortex Mixer
Reading Method	Visible Light Transmission	Fluorescence
Results		
***C. difficile* ToxinotypesTested**	**0 (A+/B+)** **III (A+/B+)** **V (A+/B+)** **VIII (A-/B+)** **X (A-/B+)** **XII (A+/B+)** **IX/XXIII (A+/B+)**	**0 (A+/B+)** **III (A+/B+)** **V (A+/B+)** **VIII (A-/B+)** **XII (A+/B+)**
Results Interpretation	INVALID POSITIVE NEGATIVE	Toxigenic *C. difficile* POSITIVE Toxigenic *C. difficile* NEGATIVE INVALID ERROR NO RESULT

Performance Comparison, Non-clinical Tests:

Interference Testing

Selected drugs and other non-microbial substances that might be present in stool samples from healthy persons or patients suspected of having *C. difficile* associated disease were added to a natural negative and a contrived positive sample. The natural negative and contrived positive samples were prepared from donor samples and were confirmed negative by cytotoxic bacterial culture. The contrived positive sample was prepared by spiking a confirmed negative sample with toxinogenic *C. difficile* strain VPI 10463 to 18 CFU/test, slightly above the 16 CFU assay limit of detection for this organism. Potentially interfering substances were added at final concentrations of 5% V/V or greater. Dilution Controls for each sample were prepared by adding a phosphate-buffered saline solution in place of the potentially interfering substance. Each sample was tested in triplicate.

The following substances, at the specified saturated solvent/diluents concentrations, do not interfere with ***illumi**gene C. difficile* test results in the final concentrations listed: Barium sulfate (5 mg/mL), fecal fat (equivalent to 2.65 mg stearic plus 1.3 mg palmitic acids per mL), hemoglobin (as methemoglobin) (3.2 mg/mL), IgA (5 mg/mL), Imodium AD® (0.00667 mg/mL), Kaopectate® (0.87 mg/mL), Metronidazole (12.5 mg/mL), mucin (3.33 mg/mL) Mylanta® (4.2 mg/mL), Pepto-Bismol® (0.87 mg/mL), Prilosec® (0.5 mg/mL), Tagamet® (0.5 mg/mL), TUMS® (0.5 mg/mL), Vancomycin (12.5 mg/mL), white blood cells (5%V/V), whole blood (5% V/V).

Cross-reactivity Study

Potentially cross-reactive microorganisms that might be present in stool samples from healthy persons or patients suspected of having *C. difficile* associated disease were added to a natural negative and a contrived positive sample. The natural negative and contrived positive samples were prepared from donor samples and were confirmed negative by cytotoxic bacterial culture. The contrived positive sample was prepared by spiking a confirmed negative sample with toxinogenic *C. difficile* strain VPI 10463 to 18 CFU/test, slightly above the 16 CFU assay limit of detection for this organism. Potentially cross-reactive microorganisms were added at concentrations of 1.2×10^8/mL (bacteria and fungi) or $1 \times 10^{5.29}$/mL $TCID_{50}$/mL (viruses). Dilution Controls for each sample were prepared by adding a phosphate-buffered saline solution in place of the potentially cross-reactive microorganisms. Each sample was tested in triplicate.

The following microorganisms, at the indicated concentrations, do not interfere with ***illumi**gene C. difficile* test results:
Aeromonas hydrophila, Bacteroides fragilis, Campylobacter coli, Campylobacter fetus, Campylobacter jejuni, Candida albicans, Citrobacter frendii, Clostridium sordellii, Clostridium perfringens, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Escherichia coli O157:H7, Escherichia fergusonii, Escherichia hermannii, Helicobacter pylori, Klebsiella pneumoniae, Lactococcus lactis, Listeria monocytogenes, Peptostreptococcus anaerobius, Plesiomonas shigelloides, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas fluorescens, Salmonella Groups B-E, *Serratia liquefaciens, Serratia marcescens, Shigella boydii, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Vibrio parahaemolyticus, Yersinia enterocolitica,* Adenovirus Types 40 and 41, Coxsackievirus, Echovirus, Rotavirus.

Performance Comparison, Clinical Tests:

Clinical trials for the ***illumi**gene C. difficile* assay, including the ***illumi**pro-10* Automated Isothermal amplification and detection system, were conducted in 2010. Performance characteristics of the ***illumi**gene C. difficile* assay were determined by comparison to cytotoxic bacterial culture. Four independent clinical test sites located in the Midwestern and Southern regions of the United States and the manufacturer evaluated a total of 697 qualified patient samples. Samples were collected from 274 (39.3%) males and 419 (60.1%) females. In the case of 4 (0.6%) of the patients, sex was not known. The age groups of patients range from 2 years of age to 96 years. No differences in test performance were observed based on patient age, sex, or geographical location. Overall Sensitivity was determined to be 95.2% (95% CI: 89.2% - 97.9%). Overall Specificity was determined to be 95.3% (95% CI: 93.2% - 96.7%). Subsequent tables show overall assay performance as well as performance by clinical site and patient age.

Table 1. Overall performance data

Cytotoxic bacterial culture	*illumigene C. difficile*		
	Positive	**Negative**	**Total**
Positive	99	5**	104
Negative	27*	546	573
Total	126	551	677
			95% CI
Sensitivity	99/104	**95.2%**	89.2 - 97.9%
Specificity	546/573	**95.3%**	93.2 - 96.7%
Correlation	645/677	**95.3%**	93.4 - 96.6%

* *15/27 false positive results were positive by another FDA cleared molecular assay. Of the remaining 12 false positive results, 8 were positive by an FDA cleared assay for the detection of GDH.*

** *2/5 false negative results were negative by another FDA cleared molecular assay*

Table 2. Performance characteristics by site

Site	**Positive Samples**			**Negative Samples**		
	illumigene **Cytotoxic bacterial culture**	**Sensitivity %**	**95% CI**	***illumigene*** **Cytotoxic bacterial culture**	**Specificity %**	**95% CI**
Total	**99/104**	**95.2%**	**89.2 – 97.9%**	**546/573**	**95.3%**	**93.2 – 96.7%**
Site 1	4/5	80.0%	37.6 – 96.4%	58/60	97.6%	88.6 – 99.1%
Site 2	12/12	100%	75.7 – 100%	62/67	92.5%	83.7 – 96.8%
Site 3	20/20	100%	83.9 – 100%	87/92	94.6%	87.9 – 97.7%
Site 4	8/8	100%	67.6 – 100%	36/39	92.3%	79.7 – 97.3%
Site 5	55/59	93.2%	83.8 – 97.3%	303/315	96.2%	93.5 – 97.8%

Table 3. Invalid rates by site

Site	**Clinical Site Evaluation**			
	Total Invalids	**Assay Invalids**	**Instrument Invalids**	**Invalid Rate**
Site 1	3	3	0	3/68 (4.4%)
Site 2	1	0	1	1/80 (1.3%)
Site 3	8	1	7	8/120 (6.7%)
Site 4	1	1	0	1/48 (2.1%)
Site 5	7	6	1	7/381 (1.8%)
Total	**20**	**11/697 (1.6%)*** **	**9/697 (1.3%)**	**20/697 (2.9%)**

*** *1 Specimen remained invalid after repeat testing from the original sample.*

Table 4. Results by patient age

Patient age	**Positive Samples**			**Negative Samples**		
	illumigene **Toxigenic culture**	**Sensitivity %**	**95% CI**	***illumigene*** **Toxigenic culture**	**Specificity %**	**95% CI**
≥ 2 - 12 years	10/11	90.9%	62.3 – 98.4%	75/79	94.9%	87.7 – 98.0%
> 12 to 21 years	5/5	100%	56.6 – 100%	53/56	94.6%	85.4 – 98.2%
> 21 years	83/87	95.4%	88.8 – 98.2%	417/437	95.4%	93.0 – 97.0%
Age Unknown	1/1	100%	20.7 – 100%	1/1	100%	20.7 – 100%

Analytical Sensitivity

The analytical sensitivity of this assay for *C. difficile* was based on 20 replicates for each measurand and with a stated probability (e.g., 95% or 19/20 positive replicates) of obtaining positive responses at the following levels of the measurands:

Strain ID	Toxinotype	Phenotype	LoD/Test
VPI 10463	0	A+/B+	4 CFU/test
2007431	III (NAP1)	A+/B+	32 CFU/test
CF1	VIII	A-/B+	64 CFU/test
2006240	V (NAP7)	A+/B+	32 CFU/test
BI8	III	A+/B+	64 CFU/test
2007858	IX/XXIII	A+/B+	32 CFU/test
8864	X	A-/B+	64 CFU/test

Additional *C. difficile* stock cultures from different sources were tested and produced positive reactions at 64 CFU/test with ***illumigene C. difficile***. Strains and toxinotypes tested were as follows: **Type 0 Strains:** 10463, 2004111, 2004205, 2005070, 2005257, 2008029, 2008162, 2008341, 2008351, 2009066, 2009099, B1, G1, J7, K12, Y1; **Type III Strains:** 2004052, 2004118, 2007431, BI17, BI8; **Type V Strains:** 2005325, 2006240, 2008188, 2009018, 2009065, BK6; **Type VIII Strains:** 43598, 2008016, CF1; **Type X Strains:** 8864; **Type XII Strains:** 2007435; **Type IX/XXIII Strains:** 2007858; **Unknown Strains:** 2009132, 2009155, 2009277.

Reproducibility

Blind coded panels of 10 samples were supplied to three independent laboratories for precision studies. Samples were randomly sorted within each panel to mask sample identities. The panels included contrived samples manufactured at the assay limit of detection (n = 3) and just below the limit of blank (i.e., high negative sample, n = 3). The panels also included uncharacterized positive (n = 2) and negative (n = 2) samples. Testing was performed by different operators at each site on the same day (intra-assay variability) for five days (inter-assay variability). Three lots of ***illumigene C difficile*** were used in this study. The results are given in the table below:

	Site 1		Site 2		Site 3		Total	
Sample Type	**Percent agreement**		**Percent agreement**		**Percent agreement**		**Percent agreement**	
Negative	20/20	100%	20/20	100%	19/19****	100%	59/59	100%
High Negative	25/30	83%	29/30	97%	28/30	93%	82/90	91%
Low Positive	30/30	100%	30/30	100%	30/30	100%	90/90	100%
Positive	20/20	100%	20/20	100%	20/20	100%	60/60	100%

**** *1 specimen generated an instrument invalid test result.*

Conclusions

The ***illumigene C. difficile*** assay used in conjunction with the ***illumipro-10*** can be used to detect toxigenic *C. difficile* in human stool samples. The test is diagnostic for toxigenic *C. difficile* infection.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Document Mail Center – WO66-0609
Silver Spring, MD 20993-0002

Meridian Bioscience, Inc.
c/o Michelle L. Smith
Senior Director, Quality Systems
3471 River Hills Dr.
Cincinnati, OH 45244

JUL 9 2010

Re: K100818

Trade/Device Name:	Illumigene C. *difficile* Assay
Regulation Number:	21 CFR §866.2660
Regulation Name:	Microorganism differentiation and identification device
Regulatory Class:	Class I
Product Code:	OMN
Dated:	June 21, 2010
Received:	June 22, 2010

Dear Ms. Smith:

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 additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. 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 Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOffices/ucm115809.htm for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. 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,

Sally A. Hojvat, M.Sc., Ph.D.
Director
Division of Microbiology Devices
Office of *In Vitro* Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

Indication(s) for Use Form

510(k) Number (if known): K100818

Device Name: ***illumigene*** Molecular Diagnostic Test System (***illumigene*** *C. difficile* DNA Amplification Assay, ***illumipro-10***)

Indications for Use:

The ***illumigene*** *C. difficile* DNA amplification assay, performed on the ***illumipro-10,*** is a qualitative *in vitro* diagnostic test for the direct detection of toxigenic *C. difficile* in human stool specimens from patients suspected of having *Clostridium difficile*-associated disease (CDAD).

The ***illumigene*** *C. difficile* assay utilizes loop-mediated isothermal DNA amplification (LAMP) technology to detect the pathogenicity locus (PaLoc) of toxigenic *Clostridium difficile*. The *Clostridium difficile* PaLoc is a gene segment present in all known toxigenic *C. difficile* strains. The *C. difficile* PaLoc codes for both the Toxin A gene (*tcdA*) and the Toxin B gene (*tcdB*), has conserved border regions, and is found at the same site on the *C. difficile* genome for all toxigenic strains[3]. The ***illumigene*** *C. difficile* assay detects the PaLoc by targeting a partial DNA fragment on the Toxin A gene. The *tcdA* target region was selected as an intact region remaining in all known A+B+ and A-B+ toxinotypes.

illumigene *C. difficile* is intended for use in hospital, reference or state laboratory settings. The device is not intended for point-of-care use.

Prescription Use ___X____ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

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

510(k) K10 0818