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

I Background Information:

A 510(k) Number
K192817

B Applicant
Meridian Bioscience, Inc.

C Proprietary and Established Names
Curian HpSA, Curian Analyzer

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
LYR	Class I, reserved	21 CFR 866.3110 - *Campylobacter fetus* Serological Reagents	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:
To obtain a substantial equivalence determination for the detection of *Helicobacter pylori* antigens in human stool.

B Measurand:
H. pylori antigen

C Type of Test:
Lateral flow fluorescent immunoassay (FIA)

III Intended Use/Indications for Use:

A Intended Use(s):
See Indications for Use below.

B Indication(s) for Use:

Curian HpSA, for use with the Curian Analyzer, is a rapid, qualitative, fluorescent immunoassay for the detection of *Helicobacter pylori* antigen in human stool. Test results are intended to aid in the diagnosis of *H. pylori* infection and to demonstrate loss of *H. pylori* antigen following treatment. Accepted medical practice recommends that testing by any current method, to confirm eradication, be done at least four weeks following completion of therapy. Test results should be taken into consideration by the physician in conjuction with the patient history and symptoms.

C Special Conditions for Use Statement(s):
Rx - For Prescription Use Only

D Special Instrument Requirements:
The Curian HpSA assay can only be run on the Curian Analyzer.

IV Device/System Characteristics:

A Device Description:
The Curian HpSA assay consists of a test strip enclosed in a plastic frame (test card). The test card contains a test line and control line. The Curian HpSA assay utilizes antibodies specific for *H. pylori* antigen in human fecal specimens. The *H. pylori* antigen (if present) binds to the *H. pylori* detector antibody conjugated to fluorescent particles, forming a complex. As the sample moves through the test strip, the *H. pylori* capture antibody, bound to the assay membrane at the test line of the strip, binds the complex and yields a fluorescent test line. As the mobile phase continues to move further up the test card, the control capture antibody, bound to the assay membrane at the control line of the strip, binds the control detector antibody conjugated to fluorescent particles. A line at the control position of the test strip should be present each time a sample or external control is tested. If the control line is not generated, adequate sample flow has not occurred, and the Curian Analyzer will consider the test invalid.

B Principle of Operation:

See **Section IV.A** above.

C Instrument Description Information:

Modes of Operation	**Yes**	**No**
Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?	☒	☐
Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?	☐	☒
Software		
FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types.	☒	☐

1. Instrument Name:
   Curian Analyzer

2. Specimen Identification:
   Specimen identification information is entered on the Curian Analyzer using the onscreen keyboard.

3. Specimen Sampling and Handling:
   Following specimen collection, a Curian HpSA sample collection brush is placed by the user into a stool specimen to coat the bristles of the brush, which is then inserted into an uncapped Curian HpSA Aioprep sample preparation device (included with the Curian HpSA assay). After insertion into the Aioprep, the handle of the collection brush is snapped off, the Aioprep device is recapped, and vortexed for five seconds. Using both hands, the user squeezes the Aioprep to add seven drops of patient specimen/reagent into the sample port of the Curian HpSA test card. If operating the Curian Analyzer in the "Incubate and Analyze" mode, the test card is inserted into the Curian Analyzer, after which all further steps are automated. If operating the analyzer in "Analyze Now" mode, the test card is incubated at 19-27ºC on the benchtop for 20 minutes before insertion into the Curian Analyzer. If a patient specimen cannot be tested immediately/ as soon as possible after collection, the specimen may be held for up to 72 hours at 2-8ºC or frozen for up to 14 days at -20ºC prior to testing.

4. Calibration:
   The Curian Analyzer is factory calibrated and does not require calibration or adjustments by the end user during day-to-day operations. See section 5 below.

5. Quality Control:

   Curian Analyzer Controls

   Internal Control
   The analyzer automatically performs a self-test to monitor internal functions, including operation of the onboard computer, integrity of the file system, available memory, and power regulation. The self-test is automatically performed each time the analyzer is turned on, every 24 hours during operation, and at wakeup after more than 24 hours of being idle. If the self-test fails, a warning or fault message will be displayed. In the case of warnings, the user may proceed with testing but should address the warning according to the Curian Analyzer package insert Operator's Manual recommendations. In the case of faults, the user will be locked out of testing until the item is resolved.

   External Control
   An instrument check (IC) is performed to confirm proper function of the Curian Analyzer's optical system and analytical capabilities. To perform an instrument check, a fluorescent IC card is inserted into the analyzer and read. An IC must be performed at least once every 30 days. If this time period has been exceeded or the IC test fails, users will be locked out of testing until the IC test is re-run and passed.

V Substantial Equivalence Information:

A Predicate Device Name(s):
PREMIER Platinum HpSA PLUS

B Predicate 510(k) Number(s):
K182559

C Comparison with Predicate(s):

Similarities		
Device & Predicate Device(s):	Curian HpSA, Curian Analyzer K192817 (Device)	PREMIER Platinum HpSA PLUS K182559 (Predicate)
Intended Use/Indications for Use	Curian HpSA, for use with the Curian Analyzer, is a rapid, qualitative, fluorescent immunoassay for the detection of *Helicobacter pylori* antigen in human stool. Test results are intended to aid in the diagnosis of *H. pylori* infection and to demonstrate loss of *H. pylori* antigen following treatment. Accepted medical practice recommends that testing by any current method, to confirm eradication, be done at least four weeks following completion of therapy. Test results should be taken into consideration by the physician in conjuction with the patient history and symptoms.	The Premier Platinum HpSA PLUS enzyme immunoassay (EIA) is an *in vitro* qualitative procedure for the detection of *Helicobacter pylori* antigens in human stool. Test results are intended to aid in the diagnosis of *H. pylori* infection and to monitor response during and post-therapy in patients. Accepted medical practice recommends that testing by any current method, to confirm eradication, be done at least four weeks following completion of therapy.
Measurand	*H. pylori* stool antigen	Same
Specimen Type	Unpreserved human stool	Same
Intended Use Population	Persons suspected of having *H. pylori* infection	Same
Type of Test	Qualitative	Same
Quality Control	Positive and Negative Controls are provided in the kit	Same
Kit Storage	Refrigerated (2 – 8ºC)	Same

Differences		
Device & Predicate Device(s):	Curian HpSA, Curian Analyzer K192817 (Device)	PREMIER Platinum HpSA PLUS K182559 (Predicate)
Technology	Fluorescent immunoassay (FIA)	Enzyme immunoassay (EIA)
Format	Single use lateral flow cassette	Microwell plate
Read Method	Curian Analyzer	Visual or Spectrophotometric
Time to Result	20 minutes	15 minutes

VI Standards/Guidance Documents Referenced:

- IEC 19-18. Safety Requirements for Electrical Equipment for Measurement, Control, and Laboratory Use – Part 1: General Requirements [Including Corrigendum 1 (2011)]. Version – IEC 61010-1. Third Edition. 2010.
- IEC. Safety Requirements for Electrical Equipment for Measurement, Control, and Laboratory Use – Part 2-101: Particular Requirements for In Vitro Diagnostic (IVD) Medical Equipment. Version 61010-2-101. 2015.
- ISO 5-40. Medical Devices – Application of Risk Management to Medical Devices. Version 14971. 2007 (R) 2010.
- ISO. In Vitro Diagnostic Medical Devices – Evaluation of Stability of In Vitro Diagnostic Reagents. Version 23640. 2015.
- IEC 19-8. Medical Electrical Equipment – Part 1-2: General Requirements for Basic Safety and Essential Performance – Collateral Standard: Electromagnetic Disturbances – Requirements and Tests. Version 60601-1-2. 2014.
- Electrical Equipment for Measurement, Control, and Laboratory Use - EMC Requirements. Version 61326-1. 2013.
- Electrical Equipment for Measurement, Control, and Laboratory Use - EMC Requirements - Part 2: In Vitro Diagnostic (IVD) Medical Equipment. Version 61326-2-6. 2013.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:
   Reproducibility of the Curian HpSA assay was assessed across three testing sites. Each site conducted testing using three Curian HpSA kit lots on three independent Curian Analyzers (one per site). Testing was performed by two operators per site over the course of five days for a total of 540 data points (180 per site). Each operator was supplied with a panel of blinded specimens prior to testing. The specimen panels were tested according to the Curian HpSA package insert instructions.

   Contrived panel members were prepared by spiking purified flagellar antigen (prepared from *H. pylori* ATCC 43504 type strain) into negative diluted natural stool (i.e., 70% stool, 30%

physiological saline) at antigen concentrations above, near and below the assay limit of detection for *H. pylori* antigen. Diluted natural stool matrix was used because the consistency of neat stool creates challenges when attempting to generate dilutions for analytical testing (for more information, see the matrix equivalency study described in **Section VII.B.2)**. Each panel consisted of one true negative, five high negatives (0.5x LoD), five low positives (1.5x LoD), and five moderate positive (3x LoD) samples, that were randomly sorted within each panel. Negative and positive controls were run on each day of testing.

The moderate positive and low positive panel members were positive at 99.3% (149/150) and at 98.0% (147/150), respectively. The high negative and true negative panel members were negative at 88.7% (133/150) and at 96.7% (29/30), respectively. All positive and negative controls yielded the expected result. Reproducibility was unaffected by Curian HpSA kit lot or Curian Analyzer. These results are acceptable.

2. Linearity:
   Not applicable

3. Analytical Specificity/Interference:

Cross-Reactivity and Microbial Interference
The Curian HpSA test was evaluated for cross-reactivity with the bacteria, fungi, and viruses listed in **Table 1** below. *H. pylori* purified flagellar antigen prepared as described above was spiked at 3x LoD into diluted natural stool matrix negative for *H. pylori*. Bacteria and fungi were spiked at a concentration $\geq 1.0 \times 10^7$ CFU/mL while viruses were spiked at a concentration $\geq 1.0 \times 10^5$ $TCID_{50}$ units per mL. For microbial interference testing, *H. pylori* purified flagellar antigen prepared as described above was spiked at 3x LoD into diluted stool matrix containing non-target organisms (see **Table 1)**. No cross-reactivity or microbial interference was observed.

Table 1. Organisms Evaluated for Cross-Reactivity

Organism	
Aeromonas hydrophila	*Proteus vulgaris*
Bacillus cereus	*Pseudomonas aeruginosa*
Borrelia burgdorferi	*Salmonella spp. Dublin*
Campylobacter coli	*Salmonella spp. Hilversum*
Campylobacter jejuni	*Salmonella spp. Minnesota*
Candida albicans	*Salmonella typhimurium* Group B
Citrobacter freundii	*Shigella boydii*
Clostridioides (Clostridium) difficile	*Shigella dysenteriae*
Clostridium perfringens	*Shigella flexneri*
Enterobacter cloacae	*Shigella sonnei*
Enterococcus faecalis	*Staphylococcus aureus*
Escherichia coli	*Staphylococcus aureus* Cowan 1
Escherichia coli O157:H7	*Staphylococcus epidermidis*
Escherichia fergusonii	*Yersinia enterocolitica*
Haemophilus influenzae	*Adenovirus 40*
Klebsiella pneumoniae	*Rotavirus*

Interfering Substances
The Curian HpSA test was evaluated for interfering substances with the substances and concentrations listed in **Table 2**. For this study, interfering substances were spiked at the indicated concentrations (see **Table 2**) into both negative diluted natural stool matrix and diluted natural stool matrix containing *H. pylori* purified flagellar antigen at 3x LoD. None of these substances where shown to interfere with the performance of the Curian HpSA assay.

Table 2. Interfering Substance Panel

Barium sulfate (5% w/v)	Mineral Oil (10% v/v)
Benzalkonium Chloride (1% v/v)	Mylanta (4.2 mg/mL)
Ciprofloxacin (0.25% w/v)	Naproxen Sodium (5% w/v)
Ethanol (1% v/v)	Nonoxynol-9 (1% v/v)
Hog gastric mucin (3.5% w/v)	Nystatin (1% w/v)
Human blood (40% v/v)	Palmitic acid (fecal fat) (20% w/v)
Human hemoglobin (12.5% w/v)	Pepto-Bismol (5% v/v)
Human urine (5% v/v)	Phenylephrine (1% w/v)
Hydrocortisone (1% w/v)	Prilosec OTC (5 mg/mL)
Imodium (5% v/v)	Sennosides (1% w/v)
Kaopectate (5%v/v)	Simethicone (10% v/v)
Leukocytes (0.05% v/v)	Steric acid (fecal fat) (20% w/v)
Mesalazine (10% w/v)	Tagamet (5 mg/mL)
Metronidazole (0.25% w/v)	TUMS (5 mg/mL)
MiraLAX (7% w/v)	Vancomycin (0.25% w/v)

High-Dose Hook Effect/Prozone
A high-dose hook effect (prozone) study was conducted to evaluate potential interference from high concentrations of *H. pylori* antigen. Purified *H. pylori* flagellar antigen prepared as described above was spiked into negative diluted natural stool matrix and tested in quintuplicate at concentrations ranging from 51 to 12,500 ng/mL (25– 6250x LoD). No false negative results suggestive of a high-dose hook effect were observed.

"Analyze Now" and "Incubate and Analyze" Read Modes /Temperature Study
The purpose of this study was to document testing results of the Curian HpSA assay in Incubate and Analyze and Analyze Now modes on the Curian Analyzer. In the Analyze Now mode, the cassette with loaded sample was developed for 20 minutes on the bench top before insertion into the Curian Analyzer for scanning. In Incubate and Analyze mode, the cassette was placed in the Curian Analyzer immediately and developed for 20 minutes before scanning. Additionally, testing was performed at different ambient temperatures, including each of the following environmental conditions: <19°C, 19-27°C, and >27°C.

For this study, contrived samples and clinical specimens (both positive and negative for *H. pylori*) were evaluated. Contrived samples were generated by spiking *H. pylori* purified flagellar antigen (ATCC 43504) into diluted natural stool matrix at 3x LoD. All positive and negative samples were in 100% agreement with the expected results regardless of the temperature and reading mode. This study demonstrated that the correct results can be obtained with the Curian HpSA assay when the test materials are stored and tested at temperatures from 19°C to 27°C in both Analyze Nowmode and Incubate and Analyze modes on the Curian Analyzer.

4. Assay Reportable Range:
   Not applicable

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

Curian HpSA Assay Controls

Internal Control
Each Curian HpSA test strip contains an internal control line to confirm correct sample flow and active reagents for the test run. If the internal control line fluorescence does not meet or exceed the cut-off level, the result is considered invalid and the test should be repeated.

External Controls
The Curian HpSA kit instructions recommend that external positive and negative controls are tested with each new kit shipment. One vial of positive control reagent (inactivated *H. pylori* purified antigen) is provided with each test kit, and the kit sample diluent buffer serves as the negative control. The positive and negative controls are intended to ensure that the kit is functional to produce the expected results. The kit should not be used if either external control fails to deliver the correct test results.

Sample Stability
Studies were conducted to examine the stability of stool samples when stored refrigerated at 2-8ºC or frozen at -20º. Negative stool samples and contrived positive samples were stored either refrigerated or frozen/thawed and tested over time with the Curian HpSA assay on the Curian Analyzer. The positive samples consisted of *H. pylori* flagellar antigen (ATCC 43504) spiked into negative diluted natural stool matrix at moderate positive (5x LoD), low positive (2x LoD), and high negative (<1x LoD) concentrations. The study results supported the package insert recommendation that stool samples can be stored for up to three days refrigerated at 2-8ºC, up to 14 days frozen at -20ºC, and that stool samples stored at -20ºC can undergo up to two freeze/thaw cycles.

6. Detection Limit:

Limit of Detection (LoD)
The limit of detection (LoD) for the Curian HpSA test was determined by spiking purified *H. pylori* flagellar antigen prepared as described above into negative diluted natural stool matrix. The initial LoD was established by testing each of five dilutions in triplicate. The initial LoD concentrations were confirmed by testing an additional 20 replicates at the target concentrations. The LoD was defined as the lowest concentration at which 95% or more of the replicates were positive. The LoD for the Curian HpSA test was determined to be 2 ng/mL for *H. pylori* ATCC 43504.

Inclusivity Study
The reactivity of four additional *H. pylori* strains (see below) was evaluated for the Curian HpSA assay. Samples were prepared by spiking negative diluted fecal matrix with each *H. pylori* strain at 3x LoD. All strains were detected at 3x LoD except for *H. pylori* strain ATCC 700392, which was detected at 6x LoD.

***H. pylori* strains**
ATCC 700392 (clade hpEurope)
ATCC 700824 (clade hpAfrica1)
CCUG 38771
CCUG 19087

7. Assay Cut-Off:
To determine the preliminary cut-off the Curian HpSA assay read on the Curian Analyzer, a panel of clinical negative and contrived positive (1x LoD) stool samples were evaluated. The initial cut-off was validated during the Method Comparison Study by testing a prospective population of 542 specimens, of which 73 were positive and 452 were negative by the Curian HpSA assay. The results of the cut-off study were found to be acceptable.

8. Accuracy (Instrument):
Not applicable

9. Carry-Over:
Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:
The performance of the Curian HpSA assay was evaluated in a multi-site prospective Method Comparison Study. Three sites in the U.S. used leftover, unpreserved stool specimens from patients suspected *of H. pylori* infection and tested the samples with the Curian HpSA.

The Curian HpSA assay results were compared to results from an FDA-cleared *H. pylori* stool antigen EIA. Performance of the FDA-cleared comparator EIA was previously established in comparison to an endoscopy biopsy composite reference method (i.e., culture, histology, and RUT) for initial *H. pylori* diagnosis with demonstrated high performance. The performance of the Curian HpSA assay was reported as positive percent agreement (PPA) and negative percent agreement (NPA) with the FDA-cleared comparator EIA results.

A total of 542 stool specimens from the intended use population were tested in the study. The ages of patients ranged from 1 to 93 years. Of the 542 patients tested, 40.6% (220) were male, and 59.4% (322) were female.

Performance of the Curian HpSA assay is shown in **Table 3**. The Curian HpSA exhibited a positive percent agreement (PPA) of 96.1% and a negative percent agreement (NPA) of 97.0%. No difference in test performance was observed based on patient age or gender. These results were acceptable.

Table 3. Method Comparison Performance of the Curian HpSA Assay

		FDA-Cleared *H. pylori* Antigen EIA		
		Positive	**Negative**	**Total**
Curian HpSA Assay	**Positive**	73	14[b]	87
	Negative	3[a]	452	455
	Total	76	466	542

a. 2/3 Curian HpSA false negatives were dispositioned as negative by PCR
b. 8/14 Curian HpSA false positives were dispositioned as positive by PCR

			95% CI
PPA	96.1%	(73/76)	89.0% to 98.6%
NPA	97.0%	(452/466)	95.0% to 98.2%

***H. pylori* antigen detection following treatment**

To support the Curian HpSA assay claim that it can be used to "demonstrate loss of *H. pylori* antigen following treatment", FDA considered evidence from the scientific literature and information from prior FDA reviews and determined that the evidence was sufficient to support this claim based on the following rationale:

- To our knowledge, there has not been published scientific literature to suggest that *H. pylori* flagellar antigen (the antigenic target of *H. pylori* stool antigen tests) varies between initial diagnosis and post-therapy (≥4 weeks after treatment) populations.
- The Curian HpSA and the predicate/comparator assay are technologically similar, i.e., they are both immunoassays, and they both incorporate similar monoclonal detector and conjugate antibodies for detection of *H. pylori* flagellar antigen. The monoclonal antibodies used in the Curian HpSA and the predicate are the most significant contributor to device performance for this assay; thus, it is expected that these assays will perform similarly in post-therapy patients.
- Review of published literature submitted by the sponsor in support of this claim includes numerous prior clinical studies with the predicate/comparator assay tested in both initial diagnosis and post-therapy cohorts and confirmed that the predicate performs similarly in both patient populations.

Based on this information, it was determined that it is appropriate to include claims for antigen detection for both pre- and post-treatment populations (i.e., initial diagnosis and post-therapy) in the Intended Use for the Curian HpSA.

2. Matrix Comparison:

An equivalency study was conducted to demonstrate that diluted natural stool matrix (i.e., liquid) was equivalent to undiluted natural matrix (i.e., solid or semi-solid stool) and was therefore suitable for use in analytical studies conducted in support of the Curian HpSA assay. Diluted stool matrix was used because the consistency of neat stool creates challenges when attempting to generate dilutions for analytical testing.

For this study, diluted natural stool matrix was generated by mixing unpreserved human stool with physiological saline to form a mixture containing 70% stool and 30% saline. Purified *H. pylori* flagellar antigen prepared as described above was spiked into each matrix at a

concentration of 3x LoD to generate 20 samples per matrix. Each sample was then tested with the Curian HpSA assay.

All diluted natural stool matrix and clinical matrix samples yielded positive results on the Curian HpSA test at this test concentration. Results of this testing demonstrated equivalence of the diluted matrix with clinical matrix and support the use of this matrix in all analytical studies.

C Clinical Studies:

1. Clinical Sensitivity:
   Not applicable

2. Clinical Specificity:
   Not applicable

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):
   Not applicable

D Clinical Cut-Off:
Not applicable

E Expected Values/Reference Range:
Studies on the epidemiology of *H. pylori* have shown that this organism is present worldwide. Gastritis caused by *H. pylori* has been shown to correlate with age, ethnic background, family size and socioeconomic class. The prevalence of *H. pylori* infection in a given population can vary from 20% to 90%. In patients diagnosed with duodenal ulcers it has been shown in every age group to be approximately 80%.

The Curian HpSA assay detects the presence of *H. pylori* antigens in human stool. The rate of positivity may vary depending on geographic location, method of specimen collection, handling and transportation, test employed and general health environment of the patient population under study.

F Other Supportive Instrument Performance Characteristics Data:
Not applicable

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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