K062948

Confidential

5.0 510(k) Summary or 510(k) Statement

DEC - 8 2006

As required by 21 CFR Section 807.92(c).

Submitted by:	Cepheid 904 Caribbean Drive Sunnyvale, CA 94089 Phone number: (408) 400-8230 Fax number: (408) 541-6439
Contact:	Russel K. Enns, Ph.D.
Date of Preparation:	September 27, 2006
Device:	
Trade name:	Cepheid Smart GBS™ Assay
Common name:	Group B Strep Assay
Classification name:	Nucleic Acid Amplification Assay System, Group B Streptococcus, Direct Specimen Test
Regulation number:	866.3740
Procode:	NJR
Classification Advisory Committee	Microbiology
Predicate Device:	IDI-Strep B Assay [510(k) no. K022504]

Device Description:
The Cepheid Smart GBS Assay is a rapid, DNA test for detecting GBS DNA from vaginal/rectal swab specimens from pregnant women. The assay is performed on the automated Cepheid SmartCycler Dx System. The SmartCycler Dx System is a rapid, real-time thermal cycler used for identifying DNA or RNA from prepared biological samples. Each instrument contains 16 independently programmable modules that can perform four-color, real-time fluorometric detection. Samples are amplified and measured in the SmartCycler's proprietary, scalable reaction tubes that are designed to optimize rapid thermal transfer and optical sensitivity.

The four channel optics in the SmartCycler Dx System enables the simultaneous detection of four targets within a single sample (multiplex assays) by employing multiplex PCR techniques and real-time fluorescent technologies such as Molecular Beacons and TaqMan® probes, Amplifluor® and Scorpion® primers, and intercalating dyes.

The Smart GBS Assay includes an internal control (IC) to monitor the presence of inhibitors in the Polymerase Chain Reaction (PCR). The GBS primers and probe detect a unique region of the *S. agalactiae* chromosome.

A vaginal/rectal swab is collected and transported to the laboratory. Swab processing then proceeds by one of two methods (direct method or an optional enriched Lim broth method). The Smart GBS Assay includes the reagents required for sample processing (except for the Lims Broth) and the detection of the target GBS DNA. Once sample processing is completed, an aliquot is added to the reconstituted assay reagents. The resulting mixture is

placed into the SmartTube, and then loaded into the SmartCycler Dx System for real-time PCR. For quality control, an external positive and negative run control are provided in the Smart GBS Assay for each run.

Device Intended Use:
The Cepheid Smart GBS Assay performed on the Cepheid SmartCycler Dx System is a qualitative in vitro diagnostic test designed to detect Group B Streptococcus (GBS) DNA from vaginal/rectal swab specimens and Lim broth cultures. The test utilizes real-time polymerase chain reaction (PCR) for a unique gene-specific sequence amplification of *Streptococcus agalactiae* recovered from clinical samples and fluorogenic target specific hybridization for the detection of the amplified DNA. Results from the Smart GBS Assay are intended for use as a method for rapid detection of GBS colonization in antepartum and intrapartum women.

- The use of the Smart GBS for intrapartum screening should not preclude the use of other strategies (e.g., antepartum testing). Intrapartum Smart GBS results are useful to identify candidates for intrapartum antibiotic prophylaxis when administration of intravenous antibiotics is not delayed pending results.

- The Smart GBS assay does not provide susceptibility results. Culture isolates are needed for performing susceptibility testing as recommended for penicillin-allergic women.

Substantial Equivalence:
The Cepheid Smart GBS Assay is substantially equivalent to the Infectio Diagnostic Inc. IDI-Strep B assay. Both assays detect Group B Streptococcus; both assays use the Cepheid SmartCycler Dx System to determine the presence of GBS through real-time PCR amplification and fluorogenic target-specific hybridization detection; both assays recommend the use of Copan Collection and Transport Liquid Stuarts medium for specimen collection.

The Smart GBS performed on the SmartCycler Dx System also has the same intended use and many of the same technological characteristics, and reagent and instrument components as the Cepheid Xpert GBS and the GeneXpert Dx System. (For example both assays have the same primers and probe that detect the same unique DNA region of of *S. agalactiae*. Both assays utilize the I-CORE thermal cycling module for amplification and detection. The Xpert GBS Assay [510(k) No. K060540] was cleared on July 25, 2006.

Table 5-1 shows the similarities and differences between the Smart GBS and the predicate device.

Table 5-1

Similarities and Differences Between the Smart GBS™ and the IDI-Strep B™ Assay

	Smart GBS™	**IDI-Strep B™ Assay**
Regulation no. /Procode	21 CFR 866.3740 / NJR	Same
Device Classification Name	Nucleic Acid Amplification Assay System, Group B Streptococcus, Direct Specimen Test	Same
Intended Use	A qualitative *in vitro* diagnostic test designed to detect Group B Streptococcus (GBS) DNA from vaginal/rectal swab specimens and Lim broth cultures. The test utilizes real-time polymerase chain reaction (PCR) for a unique gene-specific sequence amplification of *Streptococcus agalactiae* recovered from clinical samples and fluorogenic target specific hybridization for the detection of the amplified DNA. Results from the Smart GBS Assay are intended for use as a method for rapid detection of GBS colonization in antepartum and intrapartum women. • The use of the Smart GBS for intrapartum screening should not preclude the use of other strategies (e.g., antepartum testing). Intrapartum Smart GBS results are useful to identify candidates for intrapartum antibiotic prophylaxis when administration of intravenous antibiotics is not delayed pending results. • The Smart GBS assay does not provide susceptibility results. Culture isolates are needed for performing susceptibility testing as recommended for penicillin-allergic women.	A qualitative *in vitro* diagnostic test for the rapid detection of Group B streptococcus (GBS) in vaginal/rectal specimens from antepartum or intrapartum women. The test performed on the SmartCycler® automated analyzer utilizes polymerase chain reaction (PCR) for the amplification of a *cfb* gene sequence of GBS recovered from clinical samples and fluorogenic target-specific hybridization for the detection of the amplified DNA. IDI-Strep B™ Assay can be used to establish GBS colonization status of antepartum and intrapartum women.
Organism Detection	Group B streptococcus DNA	Same

	Smart GBS™	**IDI-Strep B™ Assay**
Specimen Type	Vaginal/rectal swab	Same
Collection and Transport Medium	Copan with Liquid Stuart Medium	Same
Sample Preparation	All reagents are provided in individually packaged tubes for manual sample preparation. The sample preparation procedure requires manual pipetting, fluid transfers, vortexing and centrifugation steps.	Same
Sample Processing	Direct Method: The vaginal/rectal swab is placed in Sample Preparation Reagent and processed for real-time PCR amplification and detection. Enriched Method: The vaginal/rectal swab is placed into Lim broth and incubated overnight at 37°C, prior to being processed for real-time PCR amplification and detection.	Same as Direct Method.
Assay Platform	Cepheid SmartCycler Dx System	Same
Assay Format	Amplification: PCR with I-CORE heating and cooling module. Detection: Fluorogenic target-specific hybridization	Same
Single use	Yes; single-use Smart GBS reagent beads single-use Smart GBS reagent liquids single-use Cepheid SmartTube™ reaction tubes	Yes; single-use Cepheid SmartTube™ reaction tubes
Automated assay	Yes; amplification, detection and result interpretation	Same
Time to result	Direct Method: Approximately 75 minutes, including sample processing for the direct method. Enriched Method: Optional overnight incubation; then same as direct method.	Direct Method: Approximately 45 minutes, plus 15 minutes for sample processing for the direct method. Enriched Method: not cleared for this method.
External Run Controls	External positive and negative run controls are required and provided for each assay run	Same

	Smart GBS™	**IDI-Strep B™ Assay**
External Sample Processing Controls	Materials available commercially, but not required	Materials available commercially, but not required
Internal Assay and System Controls	Internal Control; Probe Check (all optical channels) Failures result in single sample repeat.	Internal control Site check (1 optical channel) Same
Criteria for Ct determination	Primary growth curve	2nd derivative analysis
Users	CLIA high complexity laboratories	Same
Performance Characteristics as determined in the Cepheid Clinical Studies (Protocols 105 and 108) as determined relative to culture.	Protocol 105: Direct: Sensitivity: 81.62% Specificity: 96.43% Protocol 108: Enriched: Sensitivity: 98.67% Specificity: 90.48%	As determined in the Cepheid Clinical study using the same subjects as tested with the Smart GBS™: Sensitivity: 81.52% Specificity: 95.51%
Probes	TaqMan® Probes	Molecular beacons

Non-Clinical Studies:

Analytical Sensitivity/Limit of Detection (LOD):
The analytical sensitivity was determined using 11 *Streptococcus agalactiae* strains representing nine known serotypes. Quantitated cultures were tested in four replicates. All 11 strains were detected by the Smart GBS Assay. The LOD was evaluated in a separate study using groups of swabs (n=20) spiked with GBS Serotype II (75 µL/swab) at 4 concentrations (100, 250, 500, and 750 CFU). The LOD was shown to be 750 CFU/swab (20/20 detected).

Analytical Specificity:
Analytical specificity was evaluated using 106 strains representing 28 Streptococci, 78 other species including strains phylogenetically related to *Streptococcus agalactiae*, other microflora (bacteria and yeasts) commonly found in vaginal and anal flora, and human DNA. Replicates of three were tested at 1.5 ng/25 µL reaction (~2e5 equivalent genome copies per reaction). None of the 28 Streptococcal isolates (non-GBS) tested positive. Of the remaining 78 strains, four (*Enterococcus gallinarium*, *Staphylococcus simulans*, *Micrococcus luteus*, and *Propionibacterium acnes*) were weakly positive in one of six replicates at 1.5 ng/25 µL reaction.

Clinical Studies:
Performance characteristics of the Smart GBS Assay were determined in two multi-site prospective investigational studies. The first study evaluated the Smart GBS using the

direct method. The second study evaluated the Smart GBS using enriched culture method.

The direct method study (antepartum and intrapartum subjects) was performed at six institutions and the enriched culture study (antepartum subjects only) was performed at three institutions with maternity services in the United States. Each institution had a culture-based or nucleic acid test (NAT) based screening program. Testing was done in clinical laboratories.

Study participants had to meet inclusion and exclusion criteria.

The method of reference used was the culture technique recommended by the Centers for Disease Control and Prevention (CDC): microbiological culture in selective broth medium (Lim broth, which is Todd-Hewitt broth supplemented with 15 µg/mL of nalidixic acid, and 10 µg/mL of colistin), followed by overnight incubation and subculture onto solid blood agar medium. Specific identification of colonies suggestive of GBS was done with slide agglutination tests.

The performance characteristics of the Smart GBS Assay were determined from the results of 783 maternity subjects in the direct study (363 antepartum and 420 intrapartum), and 306 antepartem maternity subjects in the enriched culture study.

Total Results:

Vaginal/rectal specimens were collected from each subject using two sets of double-marked collection swabs. One of the swabs from the first set was used in the CDC-recommended culture technique; the other swab was used for Smart GBS. The second set of double-marked swabs was divided: one swab was used in the Xpert GBS Assay on the GeneXpert Dx System, the other was used in the IDI Strep B™ Assay on the SmartCycler® System.

To minimize swab-to-swab variation, the swabs remaining from the Smart GBS Assay and the IDI Strep B Assay were both cultured. Sensitivity and specificity were calculated relative to the culture results.

Table 5-2 compares the overall results from the Smart GBS Assay run on the SmartCycler Dx System and the CDC-recommended culture technique. The sensitivity and specificity data are shown below the table.

Table 5-2

Direct Method Overall Results Comparison of Smart GBS Assay and the CDC culture technique.

		Culture		
		Positive	**Negative**	**Total**
Smart GBS	**Positive**	151	21	172
	Negative	34	568	602
	Total	185	589	774

Sensitivity: 81.6% (95% CI = 75.3% - 86.9%)
Specificity: 96.4% (95% CI = 94.6% - 97.8%)
Accuracy: 92.9% (95% CI = 90.9% - 94.6%)
Prevalence: 23.9% (95% CI = 20.9% - 27.07%)

Intrapartum Results:

Table 5-3 compares the intrapartum culture results from the Smart GBS Assay run on the SmartCycler Dx System and the CDC recommended culture technique. The sensitivity and specificity data are shown below the table.

Table 5-3

Direct Method Intrapartum Results Comparison of Smart GBS Assay and the CDC culture technique.

		Culture		
		Positive	**Negative**	**Total**
Smart GBS	**Positive**	79	9	88
	Negative	14	307	321
	Total	93	316	409

Sensitivity: 84.9% (95% CI = 76.0% - 91.5%)
Specificity: 97.2% (95% CI = 94.7% - 98.7%)
Accuracy: 94.4% (95% CI = 91.7% - 96.4%)
Prevalence: 22.7% (95% CI = 18.8% - 27.1%)

Antepartum Results:

Table 5-4 compares the antepartum results from the Smart GBS Assay run on the SmartCycler Dx System relative to the CDC-recommended culture technique. The sensitivity and specificity data are shown below the table.

Table 5-4

Direct Method Antepartum Results Comparison of Smart GBS Assay and the CDC culture technique

		Culture		
		Positive	**Negative**	**Total**
Smart GBS	**Positive**	72	12	84
	Negative	20	261	281
	Total	92	273	365

Sensitivity: 78.3% (95% CI = 68.44% - 86.2%)
Specificity: 95.6% (95% CI = 92.5% - 97.7%)
Accuracy: 91.2 % (95% CI = 87.9% - 93.9%)
Prevalence: 25.2% (95% CI = 20.8% - 30.0%)

Enriched Method Smart GBS: Antepartum Results:

Table 5-5 compares the antepartum culture results from the enriched culture method Smart GBS Assay run on the SmartCycler Dx System relative to the CDC-recommended culture technique. The sensitivity and specificity data are shown below the table.

Table 5-5

Enriched Method Overall Results: (Antepartum Only) Comparison of Smart GBS Assay and the CDC culture technique

		Culture		
		Positive	**Negative**	**Total**
Smart GBS	**Positive**	74	22	96
	Negative	1	209	210
	Total	75	231	306

Sensitivity: 98.7% (95% CI = 92.8% - 100.0%)
Specificity: 90.5% (95% CI = 85.9% - 93.9%)
Accuracy: 92.5% (95% CI = 88.9% - 95.2%%)
Prevalence: 24.5% (95% CI = 19.8% - 29.7%)

Summary of Indeterminate Result Rates:

The number of indeterminate results obtained from using the Smart GBS Assay was compared to the number obtained from using the predicate device, IDI-Strep B Assay.

In the Direct Study, the Smart GBS Assay was successful on **98.23%** (779/793) of all eligible patients, and **91.17%** (723/793) gave a result on the first attempt. There were 51

specimens retested due to failed internal control and of these 14 specimens that did not give a result on the second attempt. There were a total of 4 invalid runs (33 tests) due to failed external controls.

The IDI-Strep B Assay was successful on **99.75%** (791/793) of all eligible patients, and **95.08%** (754/793) gave a result on the first attempt. There were 12 specimens retested due to failed internal control, and of these 2 specimens did not give a result on the second attempt. There were a total of 4 invalid runs (29 tests) due to failed external controls.

In the Enriched Method Study, the Smart GBS Assay was successful on **100%** (306/306) of all eligible patients, and **98.36%** (301/306) give a result on the first attempt. There was a total of 1 invalid run (3 tests) due to failed external controls and 2 invalid specimens due to failed internal controls.

The IDI-Strep B assay was successful on **100%** (306/306) of all eligible patients, and **96.73%** (296/306) gave a result on the first attempt. There were a total of 3 invalid runs (9 tests) due to failed external controls and one unresolved specimen due to computer loss power.

Reproducibility:

A panel of four simulated specimens with varying concentrations of GBS were tested 3 times per day on 10 different days at each of the three sites (4 specimens × 3 × 10 days × 3 sites). One lot of reagent was used for the study.

Table 5-6
Summary of Reproducibility Results

Specimen ID	Site 1	Site 2	Site 3	Total Agreement	Total % Agreement
Negative	30/30	30/30	29/30	89/90	98.9%
Weak Positive	29/30	30/30	30/30	89/90	98.9%
Positive	30/30	30/30	30/30	90/90	100%
Strong Positive	30/30	30/30	30/30	90/90	100%
Total Agreement	119/120	120/120	119/120	358/360	99.4%
% Agreement	99.2%	100%	99.2%	99.4%	

Conclusions:

The results of the nonclinical and clinical studies discussed above demonstrate that the device is as safe, as effective, and performs as well or better than the predicate device and the reference method, and is substantially equivalent to the Predicate device, IDI-Strep B Assay.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

DEC - 8 2006

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Re: k062948
Trade/Device Name: Smart GBS™
Regulation Number: 21 CFR 866.3740
Regulation Name: Streptococcus Spp. Serological Reagents
Regulatory Class: Class II
Product Code: NJR
Dated: September 27, 2006
Received: September 28, 2006

Dear Dr. Enns:

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.

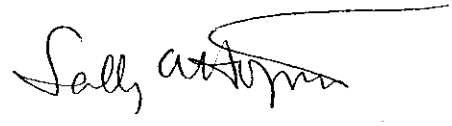
If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish 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); 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 information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (240)276-0450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,



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Enclosure

4.0 Indications for Use Statement

510(k) Number (if known): K062948

Device Name: Smart GBS™

Indications for Use:

The Cepheid Smart GBS Assay performed on the Cepheid SmartCycler Dx System is a qualitative in vitro diagnostic test designed to detect Group B Streptococcus (GBS) DNA from vaginal/rectal swab specimens and Lim broth cultures. The test utilizes real-time polymerase chain reaction (PCR) for a unique gene-specific sequence amplification of *Streptococcus agalactiae* recovered from clinical samples and fluorogenic target specific hybridization for the detection of the amplified DNA. Results from the Smart GBS Assay are intended for use as a method for rapid detection of GBS colonization in antepartum and intrapartum women.

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- The Smart GBS assay does not provide susceptibility results. Culture isolates are needed for performing susceptibility testing as recommended for penicillin-allergic women.

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)

Freddie K. Poole

Division Sign-Off

Office of In Vitro Diagnostic Device Evaluation and Safety

(Optional) K062948