MAY 1 5 2000

510(K) SUMMARY

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is: K993732/S1.

1. Submitter's Identification:

Gryphus Diagnostics, L.L.C.
2800 Milan Court, Suite 235
Birmingham, AL 35211
Contact Person: Stephen C. Johnson, Ph.D.

Data Summary Prepared: October 20, 1999

2. Name of the Device:

BVBLUE™

3. Predicate Device Information:

1. Affirm/VP Identifiaction Test for *Gardnerella vaginalis and Trichomonas vaginalis*, K# 923133, Microprobe Inc.
2. Indicard® Test, K# 964015, Litmus Concepts, Inc.
3. FemExam® TestCard™ pH and Amines Tests, K# 962718, Litmus Concepts, Inc.

4. Device Description:

The BVBLUE™ Test contains a chromogenic substrate of sialidase enzyme, IBX-4041. The chromogenic substrate is provided in each of the BVBLUE™ Testing Vessels as a solution containing 0.25 mg IBX-4041 in 0.5 mL aqueous potassium acetate solution (49.0 mg/mL; 0.5 M, pH 5.5–6.0). When the solution containing the solubilized chromogenic substrate is exposed to sialidase enzyme, the substrate is hydrolyzed to yield sialic acid and IBX-4050. Upon the addition of one of more drops of the BVBLUE™ Developer Solution [an aqueous sodium hydroxide solution (40 mg/mL; 1.0 M; pH>11.0)], IBX-4050 exhibits an intense blue color. In the absence of sialidase enzyme, the chromogenic substrate is not hydrolyzed and exhibits a yellow color upon the addition of one or more drops of the BVBLUE™ Developer Solution.

Materials Provided:

10 BVBLUE™ Units per Package:

- Ten (10) BVBLUE™ Testing Vessels each containing 0.25 mg IBX-4041 component in 0.5 mL of an aqueous potassium acetate buffer solution (49.0 mg/mL; 0.5 M; pH 5.5–6.0).
- One (1) BVBLUE™ Developer Solution Tube containing 0.5 mL of an aqueous sodium hydroxide solution (40.0 mg/mL; 1.0 M; pH>11.0).
- Instructions for Use

5. Intended Use:

BVBLUE™ is an enzyme activity test for use in the detection of vaginal fluid specimens for sialidase activity, an enzyme produced by bacterial pathogens such as *Gardnerella vaginalis*, *Bacteroides* spp., *Prevotella* spp., and *Mobiluncus* spp.

BVBLUE™ is indicated for use in women suspected of having Bacterial Vaginosis (BV) infection, e.g., women with vaginal discharge typical of BV and/or women with previous history of BV, as an aid in the diagnosis of BV infection. BVBLUE™ test results should be considered in conjunction with other clinical and patient information (see Limitations of the Procedure).

For *In Vitro* Diagnostic Use Only. BVBLUE™ is indicated for professional use only and may be used at the point of care and/or in physician's offices. It is not intended for home use.

6. Comparisons to Predicate Devices:

Affirm/VP (manufactured by Becton Dickinson) evaluates patient vaginal fluid samples for the presence of *Gardnerella vaginalis* nucleic acid. *Gardnerella vaginalis* is a microorganism causative of bacterial vaginosis. Using this test, a patient vaginal fluid sample is obtained with a sterile cotton swab. A portion of the sample is transferred to a tube containing a lysis solution, thoroughly mixed, incubated at 85 °C for 10 minutes, and treated with a buffer solution. A portion of the resulting mixture is transferred to a Processor and then reacted for a period of 30 minutes to provide an identification of *Gardnerella vaginalis* nucleic acid. A positive indication for *Gardnerella vaginalis* nucleic acid is indicative of bacterial vaginosis in patients presenting bacterial vaginosis-like symptoms.

Indicard™ test (manufactured by Litmus Concepts, Inc.) evaluates patient vaginal fluid specimens for the presence of *Gardnerella vaginalis* proline imino peptidase enzyme activity. *Gardnerella vaginalis* is a microorganism

causative of bacterial vaginosis. Using this test, a patient vaginal fluid sample is obtained with a sterile cotton swab. A portion of the sample is then transferred to the Indicard™ test to evaluate for the presence of *Gardnerella vaginalis*. A positive indication for *Gardnerella vaginalis* proline imino peptidase enzyme activity is indicative of bacterial vaginosis in patients presenting bacterial vaginosis-like symptoms.

FemExam® TestCard™ (manufactured by Litmus Concepts, Inc.) evaluates patient vaginal fluid samples for elevated pH (i.e., pH >4.7) and for the presence of volatile amines in patient vaginal fluid samples. The pH and amine tests are two components of the Amsel Criteria, the Gold Standard method of clinically diagnosing patient vaginal fluid samples for bacterial vaginosis. Using this test, a patient vaginal fluid sample is obtained with a sterile cotton swab. A portion of the sample is first transferred to a section of the FemExam® TestCard™ to evaluate for elevated pH. A second portion of the sample is transferred to the card to evaluate for the presence of volatile amines. A positive indication in both the pH and amines tests is indicative of bacterial vaginosis in patients presenting bacterial vaginosis-like symptoms.

BVBLUE™ (manufactured by Gryphus Diagnostics, L.L.C.) evaluates patient vaginal fluid samples for sialidase activity, an enzyme produced by bacterial pathogens associated with Bacterial Vaginosis (BV) such as *Gardnerella vaginalis*, *Bacteroides* spp., *Prevotella* spp., and *Mobiluncus* spp. Using this test, a patient vaginal fluid sample is obtained with a sterile cotton swab. A portion of the sample is then transferred to the BVBLUE™ test and incubated for 10 minutes at 37 °C to provide identification of sialidase enzyme activity. A positive indication for sialdiase enzyme activity is indicative of bacterial vaginosis in patients presenting bacterial vaginosis-like symptoms.

7. **Discussion of Non-Clinical Tests Performed for Determination of Substantial Equilivance are as follows:**

BVBLUE™ was evaluated using analytical samples of sialidase enzyme (Sigma Chemical Co.). The BVBLUE™ Test produces a positive result when the vaginal fluid contains ≥0.25 µg sialidase enzyme [i.e., ≥ 7.64 U (units of enzyme activity)]. This performance was defined in laboratory studies employing coded sialidase solutions containing varying levels of sialidase activity. A total of 207 replicates were evaluated.

Of the 207 replicates, a total of 69/207 contained sialidase enzyme levels ≥0.25 µg (33%); and 138/207 contained sialidase enzyme levels <0.25 µg (67%).

BVBLUE™ properly identified 69/69 (100%) of confirmed positives for sialidase enzyme levels ≥0.25 µg from analytical samples. BVBLUE™ properly identified 138/138 (100%) of confirmed negatives for sialidase enzyme levels <0.25 µg from analytical samples.

Inter-operator reproducibility studies were conducted with BVBLUE™ by three individuals in a blinded study employing coded sialidase solutions of varying levels of sialidase activity. A total of 30 replicates were performed by each individual, for a total of 90 replicates.

Of the 90 replicates, a total of 18/90 contained sialidase enzyme levels of ≥0.30 µg (20%); and 72/90 contained sialidase enzyme levels of <0.30 µg (80%).

BVBLUE™ properly identified 18/18 (100%) of confirmed positives for sialidase enzyme levels ≥0.30 µg from analytical samples. BVBLUE™ properly identified 69/72 (96%) of confirmed negatives for sialidase enzyme levels <0.30 µg from analytical samples.

Real-time and accelerated stability studies were conducted with BVBLUE™. Accelerated studies conducted at 56 °C established a stability of 41 days at 56 °C. Real-time studies conducted at ambient temperature established a stability of 241 days and continuing. These real-time stability studies are continuing.

8. **Discussion of Clinical Tests Performed:**

BVBLUE™ was evaluated in two separate clinical studies.

The first clinical study was conducted by 18 site personnel and 2 company employees at 5 separate clinical sites. A total of 502 women were evaluated. The objective of this study was to define correlations between a diagnosis of bacterial vaginosis based on Amsel Criteria, the Gold Standard Method of clinically diagnosing bacterial vaginosis as recommended by the CDC, and BVBLUE™. A second objective was to determine the reproducibility of BVBLUE™ in patients with and without bacterial vaginosis. Two vaginal fluid samples were obtained from all women by contacting a sterile cotton swab with the vaginal wall (lower one-third). One swab sample was used in an evaluation for bacterial vaginosis based on Amsel Criteria and the second was used in an evaluation of BVBLUE™. A total of three vaginal fluid samples were

obtained from a subset of women attending one clinical site. The third swab sample was used to perform an independent BVBLUE™ Test. The results of the two tests were compared. Women were excluded from the study if they had used an antibiotic or antifungal agent within three days of testing. One production lot of the BVBLUE™ Test Kit was used in the clinical study.

Of the 502 clinical samples evaluated, a total of 86/502 (17%) exhibited bacterial vaginosis based on Amsel Criteria. Of these 86 samples, 73 (85%) exhibited a positive BVBLUE™ test result. Of the 502 clinical samples evaluated, a total of 416/502 (83%) did not exhibit bacterial vaginosis based on Amsel Criteria. Of these 416 samples, 375 (90%) exhibited a negative BVBLUE™ test result.

The first clinical study did not provide for the evaluation of discordant samples via a second reference method of diagnosing for bacterial vaginosis. This issue, among others, was addressed in a second clinical study.

There was a 100% correlation of results during the reproducibility testing of BVBLUE™. The reproducibility of the BVBLUE Test was conducted on a total of 50 vaginal fluid samples obtained from a total of 25 women.

The second clinical study was conducted by 4 site personnel and 1 company employee at 2 separate clinical sites. A total of 118 women were evaluated. The objective of this study was to (1) define correlations between a diagnosis of bacterial vaginosis based on Amsel Criteria, the Gold Standard Method of clinically diagnosing bacterial vaginosis as recommended by the CDC, and BVBLUE™; (2) define correlations between a diagnosis of bacterial vaginosis based on Gram's stain, a second Gold Standard Method of clinically diagnosing bacterial vaginosis, and BVBLUE™; (3) define correlations between a diagnosis of bacterial vaginosis based on Amsel Criteria OR Gram's Stain and BVBLUE™; (4) define correlations between the semi-quantitative method of identifying *Gardnerella vaginalis* morphotypes, *Prevotella* spp. morphotypes, *Bacteroides* spp. morphotypes, and *Mobiluncus* spp. morphotypes and BVBLUE™; (5) define correlation between a genital culture *for Gardnerella vaginalis*, and anaerobic culture for microorganisms including *Bacteroides* spp. and *Prevotella* spp., and BVBLUE™; (6) define the quantitative sialidase enzyme activities in vaginal fluid specimens of women with bacterial vaginosis, candidiasis, trichomoniasis, and healthy controls; and (10) define the correlations between interfering substances including blood, semen, menses, contraceptive method, and vaginal signs and symptoms, and BVBLUE™. Three vaginal fluid samples were obtained from all women by contacting a sterile cotton swab with the vaginal wall (lower one-third). One swab sample was used in an evaluation of

bacterial vaginosis based on Amsel Criteria; a second for an evaluation of bacterial vaginosis based on Gram's stain and the semi-quantitative identification of Gram's stain morphotypes; and a third for an evaluation of BVBLUE™ and quantitative sialidase enzyme activity. A total of five vaginal fluid samples were obtained from a subset of women attending two clinical sites. The fourth swab sample was used in a genital culture. The fifth swab sample was used in an anaerobic culture. Women were excluded from the study if they had used an antibiotic or antifungal agent within three days of testing. Two production lots of the BVBLUE™ Test Kit was used in the clinical study.

In the reconciled comparison of BVBLUE™ vs. Amsel Criteria in all patients, of the 118 clinical samples evaluated, a total of 31/118 (26%) exhibited bacterial vaginosis. Of these 31 samples, 30 (97%) exhibited a positive BVBLUE™ test result. Of the 118 clinical samples evaluated, a total of 87/118 (74%) did not exhibit bacterial vaginosis. Of these 87 samples, 86 (99%) exhibited a negative BVBLUE™ test result.

In the reconciled comparison of BVBLUE™ vs. Gram's stain in all patients, of the 118 clinical samples evaluated, a total of 31/118 (26%) exhibited bacterial vaginosis. Of these 31 samples, 30 (97%) exhibited a positive BVBLUE™ test result. Of the 118 clinical samples evaluated, a total of 87/118 (74%) did not exhibit bacterial vaginosis. Of these 87 samples, 86 (99%) exhibited a negative BVBLUE™ test result.

In the comparison of BVBLUE™ vs. Amsel Criteria OR Gram's Stain in all patients, of the 118 clinical samples evaluated, a total of 34/118 (29%) exhibited bacterial vaginosis. Of these 34 samples, 26 (76%) exhibited a positive BVBLUE™ test result. Of the 118 clinical samples evaluated, a total of 84/118 (71%) did not exhibit bacterial vaginosis. Of these 84 samples, 82 (98%) exhibited a negative BVBLUE™ test result.

In the comparison of BVBLUE™ vs. Semi-Quantitative Identification of Morphotpyes Associates with Bacterial Vaginosis in all patients, of the 118 clinical samples evaluated, a total of 43/118 (36%) exhibited bacterial vaginosis. Of these 43 samples, 30 (70%) exhibited a positive BVBLUE™ test result. Of the 118 clinical samples evaluated, a total of 75/118 (64%) did not exhibit bacterial vaginosis. Of these 75 samples, 74 (99%) exhibited a negative BVBLUE™ test result.

In the comparison of BVBLUE™ vs. Clinically Significant Culture of Microorganisms Associated with Bacterial Vaginosis in all patients, of the 55 clinical samples evaluated, a total of 13/55 (24%) exhibited bacterial vaginosis. Of these 13 samples, 10 (77%) exhibited a positive BVBLUE™ test result. Of the 55 clinical samples evaluated, a total of 42/55 (76%) did

not exhibit bacterial vaginosis. Of these 42 samples, 35 (83%) exhibited a negative BVBLUE™ test result.

In the comparison of BVBLUE™ vs. clinical diagnosis of bacterial vaginosis, *Candidiasis*, Trichomoniasis, herpes, gonorrhea, and in healthy controls, of 255 clinical samples evaluated, a total of 50/255 (20%) exhibited bacterial vaginosis, 5/255 (2%) exhibited bacterial vaginosis and *Candidiasis*, and 2/255 (0.8%) exhibited bacterial vaginosis and Trichomoniasis. Of these samples, a total of 48/50 (96%) of those exhibiting bacterial vaginosis, 4/5 (80%) of those exhibiting bacterial vaginosis and *Candidiasis*, and 2/2 (100%) of those exhibiting bacterial vaginosis and Trichomoniasis exhibited a positive BVBLUE™ test result. Of the 255 clinical samples evaluated, a total of 1/255 (0.4%) exhibited gonorrhea, 1/255 (0.4%) exhibited herpes, 4/255 (1.6%) exhibited Trichomoniasis, 41/255 (16%) exhibited *Candidiasis*, and 151/255 (59%) were healthy controls. Of these samples, 1/1 (100%) of those exhibiting gonorrhea, 1/1 (100%) of those exhibiting herpes, 4/4 (100%) of those exhibiting Trichomoniasis, 41/41 (100%) of those exhibiting *Candidiasis*, and 142/151 (94%) of healthy controls exhibited a negative BVBLUE™ test result.

In the comparison of BVBLUE™ vs. the quantitative assessment of sialidase enzyme activity in patients with bacterial vaginosis, *Candidiasis*, Trichomoniasis, and in healthy controls, of 118 clinical samples evaluated, 27/118 (23%) exhibited bacterial vaginosis. The mean sialidase enzyme activity in these samples was 12.34 U. Of the 118 clinical samples, 59/118 (50%) were healthy controls. The mean sialidase enzyme activity in these samples was 2.70 U. Of the 118 clinical samples, 16/118 (14%) exhibited *Candidiasis*. The mean sialidase enzyme activity in these samples was 3.70 U. Of the 118 clinical samples, 3/118 (3%) exhibited Trichomoniasis. The mean sialidase enzyme activity in these samples was 1.99 U.

The cutoff precision of BVBLUE™, as determined using analytical samples of sialidase enzyme, was found to be 7.64 U. From the clinical studies, the 95% CI for patients with bacterial vaginosis (8.12–16.56 U) is significantly higher than the cutoff of BVBLUE™. The 95% CIs for patients with *Candidiasis* (2.57–4.83 U), Trichomoniasis (0.59–3.39 U), or in healthy controls (2.23–3.17 U) are significantly lower than the cutoff of BVBLUE™.

The data from this clinical study demonstrated that blood, semen, menses, contraceptive methods, vulvo vaginal signs and symptoms, and the presence of other morphotypes and microorganisms did not adversely effect the performance of BVBLUE™.

9. Conclusions:

The BVBLUE™ device has similar intended uses and similar technological characteristics as the predicate devices. Moreover, bench testing contained in this submission and clinical testing supplied demonstrate that any differences in their technological characteristics do not raise any new questions of safety or effectiveness. Thus, the BVBLUE™ device is substantially equivalent to the predicate devices in the identification of bacterial vaginosis in patient vaginal fluid samples.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

MAY 1 5 2000

Gryphus Diagnostics, L.L.C.
c/o Mr. Thomas M. Tsakeris
Devices and Diagnostics Consulting Group
16809 Briardale Road
Rockville, Maryland 20855

Re: K993732
Trade Name: BVBlue™
Regulatory Class: I Reserved
Product Code: MXB
Dated: March 7, 2000
Received: March 7, 2000

Dear Mr. Tsakeris:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we 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). 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 (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 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 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers 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,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510(k) Number (if known): K993732

Device Name: $BV_{BLUE™}$

Indications for Use:

$BV_{BLUE™}$ is an enzyme activity test for use in the detection of vaginal fluid specimens for sialidase activity, an enzyme produced by bacterial pathogens such as *Gardnerella vaginalis, Bacteroides* spp., *Prevotella* spp., and *Mobiluncus* spp.

$BV_{BLUE™}$ is indicated for use in women suspected of having Bacterial Vaginosis (BV) infection, e.g., women with vaginal discharge typical of BV and/or women with previous history of BV, as an aid in the diagnosis of BV infection. $BV_{BLUE™}$ test results should be considered in conjunction with other clinical and patient information (see Limitations of the Procedure)

For *In Vitro* Diagnostic Use Only. $BV_{BLUE™}$ is indicated for professional use only and may be used at the point of care and/or in physician's offices. It is not intended for home-use.

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K993732

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ✓ **OR Over-The-Counter Use** _____ **(Optional Format 1-2-96)**
(Per 21 CFR 801.109)