July 17, 2019

Associates of Cape Cod, Inc
Alison Skinner
Chief Operating Officer
124 Bernard East Saint Jean Drive
East Falmouth, Massachusetts 02536

Re: K191167
Trade/Device Name: Fungitell STAT
Regulation Number: 21 CFR 866.3050
Regulation Name: Beta-Glucan Serological Assays
Regulatory Class: Class II
Product Code: NQZ
Dated: April 9, 2019
Received: May 1, 2019

Dear Alison Skinner:

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. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. 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. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

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 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

for

Uwe Scherf, M. Sc., Ph.D.
Director
Division of Microbiology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

510(k) SUMMARY

1. SUBMITTER/510(K) HOLDER

Associates of Cape Cod, Inc.,
124 Bernard E. Saint Jean Drive
East Falmouth, MA 02356-4445

Contact Person: Alison Skinner, PhD
Telephone: +1.508.540.3444 Ext.1450
Fax Number: +1.508.540.8680

Date Prepared: July 10th, 2019

2. DEVICE NAME

Trade Name / Proprietary Name:	Fungitell® STAT
Common / Usual Name:	Antigen, Invasive Fungal Pathogens
Classification Name:	Beta-glucan serological assays
Regulation Number:	21 CFR Part 866.3050
Product Code:	NQZ
Device Class:	II
Panel:	Microbiology (83)

3. PREDICATE DEVICE

Proprietary Name:	Fungitell® STAT
510(k) Number:	DEN040003
Common/Usual Name:	Antigen, Invasive Fungal Pathogens
Classification Name:	Beta-glucan serological assays
Regulation Number:	21 CFR Part 866.3050
Product Code:	NQZ
Device Class:	II
Panel:	Microbiology (83)

- **Device Description**

The Fungitell® STAT assay provides a qualitative measurement of (1→3)-β-D-glucan. The assay is based upon a modification of the *Limulus* Amebocyte Lysate (LAL) pathway[1,2,3,4], **Figure 1**.

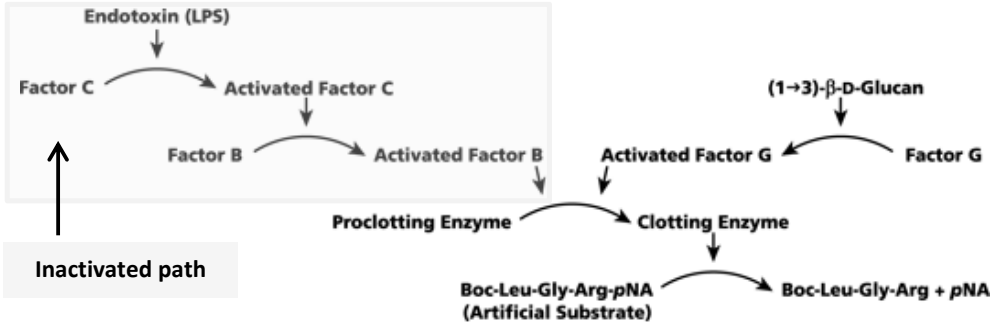

Figure 1. ***Limulus*** **Amebocyte Lysate Pathway**

The Fungitell® STAT Reagent is modified to eliminate bacterial endotoxin reactivity and, thus, to only react to (1→3)-β-D-glucan, through the Factor G-mediated side of the pathway. (1→3)-β-D-glucan activates Factor G, a serine protease zymogen. The activated Factor G converts the inactive pro-clotting enzyme to the active clotting enzyme, which in turn cleaves the para-nitroanilide substrate, Boc-Leu-Gly-Arg-pNA, creating a chromophore, para-nitroaniline (pNA), that absorbs at 405 nm. The Fungitell® STAT kinetic assay is based upon the determination of the rate of optical density increase produced by a sample. This rate is interpreted against the rate of optical density increase of the Fungitell® STAT Standard to produce an index. This patient sample index value is qualitatively interpreted as a Negative, Indeterminate or Positive result according to the index value ranges provided in **Table 1** below. The Fungitell® STAT Standard is calibrated at 80 +/- 8 pg/mL which is the Positive cut-off for the Fungitell® predicate.

Table 1: Fungitell® STAT Index Ranges

Result	Index Value Range
Negative	≤ 0.74
Indeterminate	0.75 – 1.1
Positive	≥ 1.2

- **Intended Use**

The **Fungitell® STAT** assay is a protease zymogen-based colorimetric assay for the qualitative detection of (1→3)-β-D-glucan in the serum of patients with symptoms of, or medical conditions predisposing the patient to, invasive fungal infection. The serum concentration of (1→3)-β-D-glucan, a major cell-wall component of various medically important fungi[5], can be used as an aid in the diagnosis of deep-seated mycoses and fungemias[6]. A positive result does not indicate which genus of fungi may be causing infection.

(1→3)-β-D-glucan index values should be used in conjunction with other diagnostic procedures, such as microbiological culture, histological examination of biopsy samples and radiological examination.

- **Technological Characteristics and Substantial Equivalence Discussions**

The Fungitell® STAT assay is a design modification to the Fungitell® assay format. The Fungitell® STAT assay was developed to answer the need for a single use test format and smaller kit size relative to the 96-well plate format of the predicate device Fungitell® assay.

There is an increasing incidence of fungal infections by opportunistic pathogens, especially in immuno-compromised patients[7,8,9]. Invasive fungal diseases, as opportunistic infections, are common among hematological malignancy and AIDS patients and account for a growing number of nosocomial infections, particularly among organ transplant recipients and other patients receiving immunosuppressive treatments[10,11]. Many fungal diseases are acquired by inhaling fungal spores originating from the soil, plant detritus, air-handling systems and/or exposed surfaces. Some opportunistic fungi are present in/on human skin, the intestinal tract, and mucous membranes[12,13]. Diagnosis of invasive mycoses and fungemias is usually based on non-specific diagnostic or radiological techniques. Recently, biological markers of fungal infection have been added to the available diagnostic methods[6].

Opportunistic fungal pathogens include *Candida spp*., *Aspergillus spp., Fusarium spp., Trichosporon spp., Saccharomyces cerevisiae, Acremonium spp., Coccidioides immitis, Histoplasma capsulatum*, *Sporothrix schenckii*, *Exserohilum rostratum*, and *Pneumocystis jirovecii*. The (1→3)-β-D-glucan

produced by these organisms, and others, can be detected by the Fungitell® assay[5,12,14,15].

The Fungitell® STAT device is a modified version of the Fungitell® predicate device. It has the same intended use, similar technological characteristics and is substantially equivalent to the predicate device identified in **Table 2** below. Both the Fungitell® STAT and the predicate device cover the same analytical measurement range.

Table 2. Side-by-Side Comparison of New Device (Fungitell® STAT) with Predicate Device (Fungitell®)

	Fungitell® cleared as Glucatell™ (Predicate device) DEN040003	***Fungitell® STAT (Modification of Predicate)***	***Similarity/ Difference***
Intended Use /Indications for Use	The Fungitell® assay is a protease zymogen-based colorimetric assay for the qualitative detection of (1→3)-β-D-glucan in the serum of patients with symptoms of, or medical conditions predisposing the patient to, invasive fungal infection. The serum concentration of (1→3)-β-D-glucan, a major cell-wall component of various medically important fungi[5], can be used as an aid in the diagnosis of deep-seated mycoses and fungemias[6]. A positive result does not indicate which genus of fungi may be causing infection. (1→3)-β-D-glucan titers should be used in conjunction with other diagnostic procedures, such as micro-biological culture, histological examination of biopsy samples and radiological examination.	Same	Both assays have the same Intended Use.
Assay Type	Qualitative	Same	Both assays are qualitative.

Reagent composition (major constituents)	Glucan specific LAL lysate, Boc-Leu-Gly-Arg-pNA colorimetric substrate and Tris buffer	Same	Both assays have the same reagent composition.
Scientific Technology	Spectrophotometric 96-well plate reader, capable of kinetic reading at 405 nm and, preferably, minus the background at 490 nm while maintaining a temperature of 37 ±1°C	Spectrophotometric tube reader, capable of kinetic reading at 405 nm and minus the background at 495 nm while maintaining a temperature of 37 ±1°C	Both assays use the same fundamental scientific technology but the assay format and reader methods are different.
Reagent vial format	Separate multi test vials for LAL lysate and for Pyrosol® Reconstitution Buffer	Single test vial (containing LAL lysate and buffer)	The reagent kit configurations are different.
Standard (1→3)-β-D-Glucan vial format	Multi test vial	Single test vial	The Standard kit configurations are different.
Standard (1→3)-β-D-Glucan Source	*Pachyman*	*Saccharomyces cerevisiae*	Both assays use glucan as the Standard but the organism and sources of the raw material are different. The Fungitell® STAT Standard glucan concentration is calibrated using the predicate assay glucan standard.
Assay Output	Estimated (1→3)-β-D-glucan concentration (in pg/mL) based on Fungitell® analytical measuring range of 31-500 pg/mL. Results interpreted qualitatively as Negative, Indeterminate, or Positive depending on the estimated glucan concentration.	Index value derived from the ratio of the patient sample kinetic rate (slope) over the Fungitell® STAT Standard kinetic rate. Index value analytical measuring range of 0.4 to 3.5, which is equivalent to the analytical measuring range of the Fungitell® assay (31-500 pg/mL). Results interpreted qualitatively as Negative, Indeterminate, or Positive depending on the index value.	The results and clinical interpretations are the same but the assessments are different.

- **Performance Testing**

  - *Assay Cut-off study*

The index cut-off values for the Fungitell® STAT were determined using *CLSI EP24-A2. Assessment of Diagnostic Accuracy of Laboratory Tests Using Receiver Operating Characteristics Curves; Approved Guideline- Second Edition.* Ninety three (93) de-identified patient serum samples collected for routine clinical care of the intended population were used for the study. The (1→3)-β-D-Glucan concentrations covered the full measuring range of the predicate device, Fungitell® standard curve (i.e. 31-500 pg/mL). These samples were used for the Receiver Operating Characteristics analysis of which 44 samples were Positive, 15 were Indeterminate and 34 were Negative based on the predicate device Fungitell®. The index cut-off values for Fungitell® STAT were determined to be 0.75 on the Negative side and 1.1 on the Positive side which provided the boundaries of the Indeterminate zone leading to index value ranges of ≤0.74, 0.75 - 1.1 and ≥1.2 for the Negative, Indeterminate and Positive zone, respectively.

  - *Method Comparison study*

A method comparison study was performed at a Clinical Laboratory Improvement Amendments (CLIA) laboratory using de-identified patient serum samples collected for routine clinical care of the intended population. A population of 488 de-identified patient serum samples was included in the study with (1→3)-β-D-Glucan concentrations distributed over the full range of the predicate device Fungitell® standard curve (i.e. 31-500 pg/mL). As indicated in **Table 3,** a total of 309 Negative samples, 36 Indeterminate samples and 143 Positive samples based on the predicate device Fungitell® were included in the study.

Table 3 . Two-Way Table for Fungitell® STAT and Fungitell® methods

		Fungitell® (predicate device)			
		Negative	*Indeterminate*	Positive	Total
Fungitell® STAT (New device)	Negative	283	*17*	1	301 (61.7%)
	Indeterminate	*19*	*17*	*24*	*60 (12.3%)*
	Positive	7	*2*	118	127 (26.0%)
	TOTAL	**309 (63.3%)**	***36 (7.4%)***	**143 (29.3%)**	**488 (100%)**

When samples falling within the Indeterminate zone (i.e. italic numbers within

Table 3) were excluded, there were 119 samples left for the Positive Percent Agreement (PPA) analysis and 290 samples left for the Negative Percent Agreement (NPA) analysis. The resulting PPA was 99.2%, 95% confidence interval (CI):(95.4%, 99.9%) and the NPA was 97.6%, 95% CI:(95.4%, 99.9%). If indeterminates were considered discordant results (e.g. false positives or false negatives), performance is as follows: PPA: 73.8% (118/160), 95% CI: (66.4%, 80.0%); NPA - 91.0% (283/311), 95% CI: (87.3%, 93.7%).

- *Precision/Reproducibility*

The precision/reproducibility study was performed following *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Third Edition (CLSI document EP05-A3).* The Fungitell STAT was evaluated for precision/reproducibility by spiking human serum with *Saccharomyces cerevisiae* (1→3)-β-D-Glucan to produce a panel consisting of a low negative sample, high negative sample (just below the lower cut-off of 0.74), indeterminate (equivocal) sample, low positive sample (just above the upper cut-off of 1.2) and high positive sample (~2x above the upper cut-off of 1.2). This panel was tested twice per day, in triplicate, at three sites by multiple operators over a five-day period (1 panel member x twice per day x 3 replicates x 3 sites x 5 days = 90 measurements per panel member) to determine the precision/reproducibility of the assay. Results are shown in Table 4.

The values in Table 4 are derived from the data provided by the three laboratories. The Percent Positive (% Positive) represents the number of Fungitell® STAT index values that fell within the Positive zone.

The Fungitell® STAT precision (intra-assay variation) % CV ranged from 0.4% to 26.8% and the inter-assay variation ranged from 11% to 20.44%. These % CV values are consistent with what was observed for the predicate Fungitell® assay.

Table 4. Reproducibility Study Results

Panel Member	Combined Data (3 Sites)			
	Mean Index	**Std. Dev**	**% CV**	**% Positive (Number pos./Number tested)**
Low Negative	0.56	0.11	20.44	1.1% (1/90)
High Negative*	0.75	0.08	11.07	0.0% (0/90)
Indeterminate	0.94	0.10	11.14	3.3% (3/90)
Low Positive**	1.61	0.30	18.69	96.7% (87/90)
High Positive	2.57	0.40	15.44	100% (90/90)

** Target level of < 1X (At or just below the Negative cut-off index of 0.74)*
*** Target level 1-2X (At or just above the Positive cut-off index of 1.2)*

- **References**

[1] Iwanaga, S., Miyata, T., Tokunaga, F., and Muta, T. 1992. Molecular mechanism of hemolymph clotting system in *Limulus*. Thrombosis Res. 68: 1-32.

[2] Tanaka, S., Aketagawa, J., Takahashi, S., Tsumuraya, Y., and Hashimoto, Y. 1991. Activation of a *Limulus* coagulation factor G by (1→3)-ß-D-Glucans. Carbohydrate Res. 218:167-174.

[3] Saito, H., Yoshioka, Y., Uehara, N., Aketagawa, J., Tanaka, S., and Shibata, Y. 1991. Relationship between conformation and biological response for (1→3)-ß-D-Glucans in the activation of coagulation factor G from Limulus amebocyte lysate and host-mediated antitumor activity. Demonstration of single-helix conformation as a stimulant. Carbohydrate Res. 217:181-190.

[4] Aketagawa, J., Tanaka, S., Tamura, H., Shibata, Y., and Saito, H. 1993. Activation of *Limulus* coagulation factor G by several (1→3)-ß-D-Glucans: Comparison of the potency of glucans with identical degree of polymerization but different conformations. J. Biochem 113:683-686.

[5] Odabasi, Z., Paetznick, V., Rodriguez, J., Chen, E., McGinnis, M., and Ostrosky-Zeichner, L. 2006. Differences in beta-glucan levels of culture supernatants of a variety of fungi. Medical Mycology 44: 267-272.

[6] De Pauw, B., Walsh, T.J., Donnelly, J.P. et al. 2008. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institutes of Allergy and Infectious disease Mycosis Study Group (EORTC/MSG) Concensus Group. Clin. Inf. Dis. 46: 1813-1821.

[7] Walsh, T.J., Groll, A.H. Emerging fungal pathogens: evolving challenges to immunocompromised patients for the twenty-first century. Transpl. Infectious Dis. 1999: 1:247-261.

[8] Fishman, J.A., Rubin, R.H. Infection in organ-transplant recipients. New England Journal of Medicine. 1998: 338:1741-1751.

[9] Obayashi, T., Yoshida, M., Mori, T., Goto, H. Yasuoka, A., Iwasaki, H., Teshima, H., Kohno, S., Horichi, A., Ito, A., Yamaguchi, H., Shimada, K., and Kawai, T. 1995. Plasma (1→3)-ß-D-Glucan measurement in diagnosis of invasive deep mycosis and fungal febrile episodes. Lancet. 345: 17-20.

[10] Fridkin, S.K. and Jarvis, W.R. 1996. Epidemiology of nosocomial fungal infections. Clin. Micro. Rev. 9: 499-511.

[11] . Alexander, B., Diagnosis of fungal infection: new technologies for the mycology laboratory. Transpl. Infectious Dis. 2002: 4 (Suppl. 3):32-37

[12] Lass-Florl, C. 2009. The changing face of epidemiology of invasive fungal disease in Europe. Mycoses. 52: 197-205.

[13] Nucci, M. and Anaissie, E. 2009. Fungal infections in hematopoietic stem cell transplantation and solid organ transplantation - Focus on aspergillosis. Clin. Chest Med. 30: 295-306.

[14] Litvintseva, A.P., Lindsley, M.D., Gade, L., Smith, R., Chiller, T., Lyons, J.L., Thakur, K.T., Zhang, S.X., Grgurich, D.E., Kerkering, T.M., Brandt, M.E., and Park, B,J. Utility of (1-3)-β-D-glucan testing for diagnostics and monitoring response to treatment during the multistate outbreak of fungal meningitis and other infections. J. Clin. Microbiol. 2015; 53:618-25.

[15] Odabasi, Z., Mattiuzzi, G., Estey, E., Kantarijian, H., Saeki, F., Ridge, R., Ketchum, P., Finkelman, M., Rex, J., and Ostrosky-Zeichner, L. 2004. ß-Glucan as a diagnostic adjunct for invasive fungal infections: Validation, cut-off development, and performance in patients with Acute Myelogenous Leukemia and Myelodysplastic Syndrome. CID 39: 199-205.