510(k) DECISION SUMMARY

A. 510(k) Number:

K124067

B. Purpose for Submission:

De novo request for evaluation of automatic class III designation for the VITEK®MS.

C. Measurand:

Abiotrophia defectiva	*Campylobacter coli*	*Clostridium perfringens*
Achromobacter denitrificans[1]	*Campylobacter jejuni*	*Clostridium ramosum*
Achromobacter xylosoxidans[1]	*Candida albicans*	*Corynebacterium jeikeium*
Acinetobacter baumannii complex	*Candida dubliniensis*	*Cronobacter sakazakii*
	Candida famata	*Cryptococcus neoformans*
Acinetobacter haemolyticus	*Candida glabrata*	*Edwardsiella hoshinae*
Acinetobacter junii	*Candida guilliermondii*	*Edwardsiella tarda*
Acinetobacter lwoffii	*Candida haemulonii*	*Eikenella corrodens*
Actinomyces meyeri	*Candida inconspicua*	*Elizabethkingia meningoseptica*
Actinomyces neuii	*Candida intermedia*	
Actinomyces odontolyticus	*Candida kefyr*	*Enterobacter aerogenes*
Aerococcus viridans	*Candida krusei*	*Enterobacter asburiae*[4]
Aeromonashydrophila/caviae[2]	*Candida lambica*	*Enterobacter cloacae*[4]
Aeromonas sobria[2]	*Candida lipolytica*	*Enterobacter cancerogenus*
Aggregatibacter actinomycetemcomitans	*Candida lusitaniae*	*Enterobacter gergoviae*
	Candida norvegensis	*Enterococcus avium*
Aggregatibacter aphrophilus	*Candida parapsilosis*	*Enterococcus casseliflavus*
Aggregatibacter segnis	*Candida pelliculosa*	*Enterococcus durans*
Alcaligenes faecalis ssp faecalis	*Candida rugosa*	*Enterococcus faecalis*
	Candida tropicalis	*Enterococcus faecium*
Bacteroides caccae	*Candida utilis*	*Enterococcus gallinarum*
Bacteroides fragilis	*Candida zeylanoides*	*Escherichia coli*[5]
Bacteroides ovatus	*Chryseobacterium indologenes*	*Escherichia fergusonii*
Bacteroides thetaiotaomicron	*Citrobacter amalonaticus*	*Escherichia hermannii*
Bacteroides uniformis	*Citrobacter braakii*[3]	*Ewingella americana*
Bacteroides vulgatus	*Citrobacter freundi*[3]	*Finegoldia magna*
Bordetella parapertussis	*Citrobacter youngae*[3]	*Fusobacterium necrophorum*
Bordetella pertussis	*Citrobacter koseri*	*Fusobacterium nucleatum*
Brevundimonas diminuta	*Clostridium clostridioforme*	*Gardnerella vaginalis*
Burkholderia multivorans	*Clostridium difficile*	*Gemella haemolysans*

Gemella morbillorum	*Prevotella buccae*	*Staphylococcus saprophyticus*
Geotrichum capitatum	*Prevotella denticola*	*Staphylococcus schleiferi*
Granulicatella adiacens	*Prevotella intermedia*	*Staphylococcus sciuri*
Haemophilus influenzae	*Prevotella melaninogenica*	*Staphylococcus simulans*
Haemophilus parahaemolyticus	*Propionibacterium acnes*	*Staphylococcus warneri*
Haemophilus parainfluenzae	*Proteus mirabilis*	*Stenotrophomonas maltophilia*
Hafnia alvei	*Proteus penneri*[7]	*Streptococcus agalactiae*
Kingella denitrificans	*Proteus vulgaris*[7]	*Streptococcus anginosus*
Kingella kingae	*Providencia rettgeri*	*Streptococcus constellatus*
Klebsiella oxytoca	*Providencia stuartii*	*Streptococcus dysgalactiae*
Klebsiella pneumoniae	*Pseudomonas aeruginosa*	*Streptococcus gallolyticus ssp gallolyticus*
Kodamaea ohmeri	*Pseudomonas fluorescens*	*Streptococcus infantarius ssp coli*
Lactococcus garvieae	*Pseudomonas putida*	*Streptococcus infantarius ssp infantarius*
Lactococcus lactis ssp lactis	*Pseudomonas stutzeri*	*Streptococcus intermedius*
Leclercia adecarboxylata	*Ralstonia pickettii*	*Streptococcus mitis/Streptococcus oralis*
Legionella pneumophila	*Raoultella ornithinolytica*	*Streptococcus mutans*
Leuconostoc mesenteroides	*Raoultella planticola*	*Streptococcus pneumoniae*
Leuconostoc pseudomesenteroides	*Rhizobium radiobacter*	*Streptococcus pyogenes*
Listeria monocytogenes	*Rhodotorula mucilaginosa*	*Streptococcus salivarius ssp salivarius*
Malassezia furfur	*Rothia mucilaginosa*	*Streptococcus sanguinis*
Malassezia pachydermatis	*Saccharomyces cerevisiae*	*Trichosporon asahii*
Micrococcus luteus/lylae	*Salmonella group*[6]	*Trichosporon inkin*
Mobiluncus curtisii	*Serratia fonticola*	*Trichosporon mucoides*
Moraxella (Branhamella) catarrhalis	*Serratia liquefaciens*	*Vibrio cholerae*
Morganella morganii	*Serratia marcescens*	*Vibrio parahaemolyticus*
Neisseria cinerea	*Serratia odorifera*	*Vibrio vulnificus*
Neisseria gonorrhoeae[6]	*Sphingobacterium multivorum*	*Yersinia enterocolitica*
Neisseria meningitidis	*Sphingobacterium spiritivorum*	*Yersinia frederiksenii*
Neisseria mucosa	*Sphingomonas paucimobilis*	*Yersinia intermedia*
Ochrobactrum anthropi	*Staphylococcus aureus*	*Yersinia kristensenii*
Oligella ureolytica	*Staphylococcus capitis*	*Yersinia pseudotuberculosis*
Oligella urethralis	*Staphylococcus cohnii ssp cohnii*	
Pantoea agglomerans	*Staphylococcus cohnii ssp urealyticus*	
Parvimonas micra	*Staphylococcus epidermidis*	
Pasteurella multocida	*Staphylococcus haemolyticus*	
Pediococcus acidilactici	*Staphylococcus hominis ssp hominis*	
Peptoniphilus asaccharolyticus	*Staphylococcus lugdunensis*	
Peptostreptococcus anaerobius		
Prevotella bivia		

1. *Achromobacter denitrificans* and *Achromobacter xylosoxidans* identifications should be considered as a slashline result, *Achromobacter denitrificans/ Achromobacter xylosoxidans*.
2. *Aeromonas hydrophila/caviae* and *Aeromonas sobria* should be considered as an *Aeromonas* species group identification.

3. *Citrobacter freundii, Citrobacter braakii* and *Citrobacter youngae* should be considered as *Citrobacter freundii* complex.
4. *Enterobacter cloacae* and *Enterobacter asburiae* identifications should be considered as a slashline result, *Enterobacter cloacae/ Enterobacter asburiae*.
5. *Shigella* species and *E. coli* O157 are identified as *Escherichia coli*. Confirmatory tests are required to differentiate *Escherichia coli* from *Shigella* species or *E. coli* O157.
6. Confirmatory tests recommended for *Neisseria gonorrhea* and *Salmonella* species.
7. *Proteus penneri* and *Proteus vulgaris* identifications should be considered as a slashline result, *Proteus penneri/ Proteus vulgaris*.

D. Type of Test:

A mass spectrometer system for clinical use for the identification of microorganisms is a qualitative *in vitro* diagnostic device intended for the identification of microorganisms cultured from human specimens. The device is comprised of an ionization source, a mass analyzer and a spectral database. The device is indicated for use in conjunction with other clinical and laboratory findings to aid in the diagnosis of bacterial and fungal infections.

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:

Trade Name: VITEK®MS

Common Name: VITEK MS

G. Regulatory Information:

1. Regulation Number: 21 CFR 866. 3361
2. Classification: Class II (special controls)
3. Product code: PEX
4. Panel: Microbiology (83)

H. Intended Use:

1. Intended use(s):
VITEK®MS is a mass spectrometer system using matrix-assisted laser desorption/ionization - time to flight (MALDI-TOF) for the identification of microorganisms cultured from human specimens.

The VITEK®MS is a qualitative in vitro diagnostic device indicated for use in conjunction with other clinical and laboratory findings to aid in the diagnosis of bacterial and yeast infections.

The following organisms are claimed:

Abiotrophia defectiva	*Candida inconspicua*	*Enterococcus casseliflavus*
Achromobacter denitrificans[1]	*Candida intermedia*	*Enterococcus durans*
Achromobacter xylosoxidans[1]	*Candida kefyr*	*Enterococcus faecalis*
Acinetobacter baumannii complex	*Candida krusei*	*Enterococcus faecium*
Acinetobacter haemolyticus	*Candida lambica*	*Enterococcus gallinarum*
Acinetobacter junii	*Candida lipolytica*	*Escherichia coli*[5]
Acinetobacter lwoffii	*Candida lusitaniae*	*Escherichia fergusonii*
Actinomyces meyeri	*Candida norvegensis*	*Escherichia hermannii*
Actinomyces neuii	*Candida parapsilosis*	*Ewingella americana*
Actinomyces odontolyticus	*Candida pelliculosa*	*Finegoldia magna*
Aerococcus viridans	*Candida rugosa*	*Fusobacterium necrophorum*
Aeromonashydrophila/caviae[2]	*Candida tropicalis*	*Fusobacterium nucleatum*
Aeromonas sobria[2]	*Candida utilis*	*Gardnerella vaginalis*
Aggregatibacter actinomycetemcomitans	*Candida zeylanoides*	*Gemella haemolysans*
Aggregatibacter aphrophilus	*Chryseobacterium indologenes*	*Gemella morbillorum*
Aggregatibacter segnis	*Citrobacter amalonaticus*	*Geotrichum capitatum*
Alcaligenes faecalis ssp faecalis	*Citrobacter braakii*[3]	*Granulicatella adiacens*
Bacteroides caccae	*Citrobacter freundi*[3]	*Haemophilus influenzae*
Bacteroides fragilis	*Citrobacter koseri*	*Haemophilus parahaemolyticus*
Bacteroides ovatus	*Citrobacter youngae*[3]	*Haemophilus parainfluenzae*
Bacteroides thetaiotaomicron	*Clostridium clostridioforme*	*Hafnia alvei*
Bacteroides uniformis	*Clostridium difficile*	*Kingella denitrificans*
Bacteroides vulgatus	*Clostridium perfringens*	*Kingella kingae*
Bordetella parapertussis	*Clostridium ramosum*	*Klebsiella oxytoca*
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Brevundimonas diminuta	*Cronobacter sakazakii*	*Kodamaea ohmeri*
Burkholderia multivorans	*Cryptococcus neoformans*	*Lactococcus garvieae*
Campylobacter coli	*Edwardsiella hoshinae*	*Lactococcus lactis ssp lactis*
Campylobacter jejuni	*Edwardsiella tarda*	*Leclercia adecarboxylata*
Candida albicans	*Eikenella corrodens*	*Legionella pneumophila*
Candida dubliniensis	*Elizabethkingia meningoseptica*	*Leuconostoc mesenteroides*
Candida famata	*Enterobacter aerogenes*	*Leuconostoc pseudomesenteroides*
Candida glabrata	*Enterobacter asburiae*[4]	*Listeria monocytogenes*
Candida guilliermondii	*Enterobacter cancerogenus*	*Malassezia furfur*
Candida haemulonii	*Enterobacter cloacae*[4]	*Malassezia pachydermatis*
	Enterobacter gergoviae	
	Enterococcus avium	

Micrococcus luteus/lylae	*Pseudomonas putida*	*Stenotrophomonas maltophilia*
Mobiluncus curtisii	*Pseudomonas stutzeri*	*Streptococcus agalactiae*
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Neisseria cinerea	*Raoultella planticola*	*Streptococcus dysgalactiae*
Neisseria gonorrhoeae[6]	*Rhizobium radiobacter*	*Streptococcus gallolyticus ssp gallolyticus*
Neisseria meningitidis	*Rhodotorula mucilaginosa*	*Streptococcus infantarius ssp coli*
Neisseria mucosa	*Rothia mucilaginosa*	*Streptococcus infantarius ssp infantarius*
Ochrobactrum anthropi	*Saccharomyces cerevisiae*	*Streptococcus intermedius*
Oligella ureolyticaOligella urethralis	*Salmonella group*[6]	*Streptococcus mitis/Streptococcus oralis*
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Propionibacterium acnes	*Staphylococcus epidermidis*	*Yersinia enterocolitica*
Proteus mirabilis[7]	*Staphylococcus haemolyticus*	*Yersinia frederiksenii*
Proteus penneri[7]	*Staphylococcus hominis ssp hominis*	*Yersinia intermedia*
Proteus vulgaris	*Staphylococcus lugdunensis*	*Yersinia kristensenii*
Providencia rettgeri	*Staphylococcus saprophyticus*	*Yersinia pseudotuberculosis*
Providencia stuartii	*Staphylococcus schleiferi*	
Pseudomonas aeruginosa	*Staphylococcus sciuri*	
Pseudomonas fluorescens	*Staphylococcus simulans*	
	Staphylococcus warneri	

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2. Indication(s) for use: Same as intended use.

3. Special conditions for use statement(s):

   The VITEK® MS is for prescription use only in accordance with 21 CFR 801.109.

4. Special instrument requirements:

   VITEK® MS: Shimadzu AXIMA® Assurance mass spectrometer

   VITEK® MS Prep Station

   VITEK MS-DS Target Slides

   Reagents:

   - VITEK MS-CHCA (Alpha-cyano-4-hydroxy-cinnamic acid) solution
   - VITEK MS-FA (Formic acid) reagent

   Database: VITEK® MS V2.0 Knowledge Base

   Software:
   - VITEK® MS Acquisition Station
   - VITEK® MS Prep Station
   - Myla™

I. Device Description:

The VITEK® MS v2.0 system is a system consisting of kit reagents (VITEK MS-CHCA, VITEK MS-FA), VITEK MS-DS target slides, VITEK® MS Prep Station, Knowledge Base, software, and the VITEK® MS (original equipment manufacturer (OEM)-labeled Shimadzu AXIMA® Assurance mass spectrometer).

The VITEK® MS v2.0 system includes an OEM-labeled Shimadzu AXIMA® Assurance mass spectrometer linked to a reference database, referred to as Knowledge Base. Matrix assisted laser desorption ionization (MALDI) is the process used to ionize a sample in to the gas phase. A pulsed laser beam is directed on to the sample. Energy from the laser beam desorbs and ionizes the sample. Extraction plates provide high-voltage electrical fields to accelerate the ionized particles upwards through the time-of-flight (TOF) vacuum tube. An ion lens focuses the ions. Deflector plates steer the ions on a path towards the linear detector at the top of the flight-tube. An ion gate blanks out low mass ions (for example, derived from the matrix). The detector detects the ions directly from the sample (lower-molecular weight ions followed by higher-molecular weight ions). Ions hitting the detector cause an electrical signal which is recorded. The

recorded signal is processed by the software and presented as a spectrum of intensity versus mass, in Daltons (Da).

During target ionization, mass spectra within a range of 2,000-20,000 Daltons are recorded in linear positive mode at a laser frequency of 50 Hz. For each interrogation, laser shots at different positions within the target well produce up to 100 mass profiles that are summed into a single, raw mass spectrum. The spectrum is then processed by baseline correction, de-noising, and peak detection to identify well-defined peaks. The list of these significant peaks is subjected to a proprietary process called "mass binning". The processed (binned) data are used to query the Knowledge Base to determine the unknown's taxonomic identity. These results are then provided in the form of a single, species-level (and sometimes subspecies-level) identification, a split (low discrimination) identification with up to four species-level alternatives displayed, or no identification.

VITEK MS-CHCA (Alpha-cyano-4-hydroxy-cinnamic acid) is the solution that serves as a matrix which will crystalize with the microbial sample on the target slide spot. 1.0 µl of the matrix is added to the spot with the sample and allowed to dry forming crystals.

The VITEK MS-FA (Formic acid) reagent is used to pre-treat yeast in order to extract protein before the VITEK MS-CHCA matrix is added to the spot containing the sample.

VITEK MS-DS target slides are single-use disposables which contain 3 acquisition groups of 16 sample spots. Each group includes 1 calibration spot. Target slides are for single use only.

The VITEK® MS Prep Station is used to prepare VITEK MS-DS target slides. It consists of a computer workstation equipped with a barcode reader, Touch Screen and Virtual Keyboard.

bioMérieux's VITEK®MS, is the same instrument as the Shimadzu Axima Assurance MALDI-TOF spectrometer. The VITEK®MS is manufactured for bioMérieux by Kratos Analytical (a Shimadzu subsidiary) in Manchester, UK. The VITEK®MS contains a Class 1 laser product containing a Class 3b invisible-light laser. The laser is a 337 nm nitrogen laser, fixed focus.

The Acquisition Station software operates the VITEK®MS instrument to acquire spectral data from each sample. Calibration is an automatic first step in the sample acquisition process. The Acquisition Station consists of a computer workstation equipped with a barcode reader and the Acquisition Station Software v1.4.2. The VITEK®MS is connected to the VITEK® MS Acquisition Station via USB, serial and camera ports. The recorded signal is processed by the Acquisition Station software and presented as a spectrum of intensity versus mass in Daltons (Da). After spectra have been acquired from each sample spot in an acquisition group, the calibration spot is checked again.

- The VITEK® MS Analysis Server is the software that manages the VITEK®MS workflow and computes VITEK®MS identification results. It is a software component that resides on theMyla™
Server (PC).

Myla™ is a computer application ("Middleware"), based on Web technology, which allows data

related to the laboratory workflow, laboratory instruments, Laboratory Information System (LIS), analysis results, etc. to be grouped together. Myla™ interfaces between the bioMérieux instruments connected to the application (e.g., VITEK®MS) and the Laboratory Information System (LIS). Myla™ manages the VITEK®MS workflow and computes the identification results with the use of a computation engine and organism knowledge bases.

Knowledge Base: The reference database for the VITEK®MS system includes data representing 755 taxa, including 645 bacteria and 110 fungi. Each species or species group is represented by an average of 10 isolates (range 2 - 475). In order to capture the degree of acceptable variation within spectra from the same species, each reference isolate was grown on multiple media types under several growth conditions. The raw spectra were then acquired by more than one technician using multiple instruments. This process resulted in an average of 40 reference spectra per species.

J. Standard/Guidance Document Referenced (if applicable):

Standards References

	Standards No.	Recognition Number (FDA)	Standards Title	Date
1	C5O-A		Mass Spectrometry in the Clinical Laboratory: General Principles and Guidance; Approved Guideline, 1st Edition	10/29/2007
2	MM09A	7-123	Nucleic Acid Sequencing Methods in Diagnostic Laboratory Medicine; Approved Guideline, 1st Edition	12/20/2004
3	MM-18A	7-192	Criteria for Identification of Bacteria and Fungi by DNA Target Sequencing; Approved Guideline, 1st Edition	4/28/2008
4	M35-A2	7-197	Abbreviated Identification of Bacteria and Yeast; Approved Guideline, 2nd Edition	11/24/2008
5	EP9-A2-IR	7-92	Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline; 2nd Edition (Interim Revision)	7/30/2010
6	EP12-A2	7-152	User Protocol for Evaluation f Qualitative Test Performance (2nd edition)	09/09/2008

Guidance Documents Referenced

	Title	Date
1	FDA/CDRH/ODE Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff	4/19/1998
2	Statistical Guidance on Reporting Results From Studies Evaluating Diagnostic Tests	3/13/2007

K. Test Principle:

The VITEK®MS system is based on a matrix-assisted laser desorption ionization-time of flight mass spectrometer (MALDI-TOF MS). The colony is mixed with a saturated matrix solution and forms crystals. The ionization of this mixture by the laser induces the desorption and transfer of protons from photo-excited matrix to analyte to form a protonated molecule. During the analysis process, proteins are ionized without fragmentation by the coordinated action of the laser and the small organic acids of the matrix and separated on the basis of their mass-to-charge ratios, a process which results in a characteristic mass spectral profile. Microbial identification is based on the comparison of the protein spectrum generated from intact whole bacterial cells to the knowledge database of species-specific reference protein profiles using a particular algorithm.

L. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Reproducibility

A reproducibility study was conducted at three external sites with a panel of 10 organisms. Each organism was tested in duplicate in each of two runs on the VITEK®MS, on five separate days, at each trial site for a total of 20 replicates per reproducibility organism. Samples were tested in both sequential and randomized order. Three different lots of VITEK MS-CHCA, VITEK MS-FA and VITEK MS-DS target slides were included in the study.

For all sites combined, the reproducibility of the VITEK®MS organism specific and overall rate of correct identification was 99.7% (598/600) with a CI of [98.8 ; 99.9 %].

b. Linearity/assay reportable range:

Not applicable, qualitative assay.

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Calibrator:

E. coli ATCC 8739 is used to as a calibrator. This organism is deposited with VITEK MS-CHCA matrix on positions: xA1, xB1, xC1, of the VITEK MS-DS target slides depending on the number of samples tested (one calibrator per acquisition group of 16 spots). The VITEK®MS goes to the calibration spot in an acquisition group and performs a calibration. If the calibration passes, the instrument goes to the first spot in the acquisition group. If the calibration fails, an error is reported and VITEK®MS proceeds to the next acquisition group without collecting sample spectra. After spectra have been acquired from each sample spot in an acquisition group, the calibration spot is checked again. The calibration sample should provide E. *coli* identification at 99.9% in Myla™ software.

Controls:

Two organisms are used for positive quality control. Matrix alone is used for the negative

control. The quality control strains are as follows:

	Expected Result
Enterobacter aerogenes ATCC® 13048	*Enterobacter aerogenes*
Candida glabrata ATCC MYA-2950	*Candida glabrata*
Negative Control (matrix)	No Identification

NOTE: If the negative control does not give the expected result, users need to visually inspect the surface of the VITEK MS-DS target slides to ensure the slides are clean and repeat testing with new slide.

d. Assay cut-off:

After the calibration is accepted for an acquisition group, the VITEK®MS acquires the spectra for the samples in that group. The instrument then scans the sample to acquire data. As the spectrum is acquired for each target spot, it is visible in the Spectrum Display on the Acquisition Screen with the number of profiles increasing as they are collected. A single profile is generated by 5 laser shots. The goal is to achieve 100 acceptable profiles, while 30 is the minimum number of acceptable profiles. When sufficient data has been acquired, the spectrum data is passed to the Analysis Server for analysis and the VITEK®MS goes to the next spot in the acquisition group.

A perfect match between the spectrum and the unique spectrum of a single organism or organism group would provide a percent probability of 99.9. Results are displayed as follows:

- A single identification is displayed with confidence value of 60 to 99.9 when one significant organism or organism group is retained.
- Low Discrimination identifications are displayed when more than one significant organism or organism group are retained, but not for more than 4 organisms. In this case, the sum of confidence values is equal to 100.
- When more than 4 organisms or organism groups are found, the organism is considered as non-identified. In this case, a list of possible organisms is displayed and the sum of confidence values is less than 100.
- When no match is found, the organism is considered as non-identified U-unclaimed identification

A symbol ‘U’ may appear next to some organism identifications. This VITEK®MS identification indicates that the VITEK®MS result is a non-clinically validated organism. In the interest of public health, these organisms are displayed in the VITEK®MS report as a means of directing the required additional laboratory testing. Identification of non-clinically validated organisms must be performed with an alternate laboratory method. Results for non-clinically validated organisms cannot be transmitted from the VITEK®MS to the laboratory information system.

Non-clinically validated organisms include:

- Organisms with insufficient clinical performance data.
- Organisms not found in human clinical samples as reported in the scientific literature.

e. Detection limit (LoD)

For the VITEK®MS System, the LoD study demonstrated that the LoD is different in terms of McFarland (McF) measurement depending of the tested species (i.e., *S.aureus*, *P. aeruginosa*, *E.coli*, *C.jeikeium*, and *C. glabrata*). The minimum LoD is from 2 to 6 McF *S. aureus* and *C. jeikeium* respectively and 7 McF for yeast (*C. glabrata*). The LoD study demonstrated that applying an insufficient quantity of colony usually results in no spectra being acquired. In terms of colony forming units (CFU)/spot (1 µl), the limit of detection is 10^5 CFU/spot for bacteria and 10^4 CFU/spot for yeast. Applying too much colony may cause suboptimal performance of the system. If an excessive quantity of colony is applied, the cells may not suspend well in the matrix suspension and may impact the extraction process and the subsequent crystal formation by the matrix. A 1 µl loop should be used to pick up part of a suitable colony (i.e., approximately 3 mm in size).

f. Analytical specificity:

Analytical specificity was assessed using two processes:

1. Database development: For each reference species spectrum in the database, signal preprocessing and peak detection was performed to identify peaks. Peaks in the mass spectrum between 3,000 and 17,000 Daltons were divided into 1300 pre-defined intervals called "bins". This process was replicated for each of the reference species thus creating a matrix with a species-specific weight for each of the 1300 bins. Bin scores from organism spectra are classified based on a supervised machine learning algorithm, known as the "Advanced Spectrum Classifier" (ASC), which is derived from the distribution of weighted bin scores from all spectra for a given species. By examining the ASC scores for all claimed species, it was determined that a threshold of 60% indicates that an unknown isolate's overall score is within the range of scores generated by known examples of that species, but is outside the range of scores generated by every other species in the database.

   Once an unknown organism's raw spectrum is acquired by the mass spectrometer it goes through pre-processing and mass binning as described above. The bin scores then go through an iterative process whereby the score within each bin is multiplied by the weighted bin value for each reference species in the Knowledge Base. The sum of the weighted bin scores is then calculated and used to determine the confidence value of the unknown relative to each reference species. After confidence values are obtained, the list of possible organisms is reduced using a decision analysis protocol

which is performed in order to retain only organism confidence values with scores above the predefined cut-off of a 60% confidence level and within a pre-defined ASC score tolerance. Finally, the resulting organism list is reported. In the event that there are more than four species on this list or if no species are on the list, a result of "no identification" is reported.

2. Analytical Specificity Study: To determine the discriminatory power of the VITEK®MS was evaluated with organisms that are closely related within a group and multiple strains of the same organism. Forty-three organism pairs representing 18 organism groups were evaluated in the study. This data set included 359 individual results. Overall, there were no specific trends or remarkable cross-reactivity to be noted in these results. Of the 18 organism groups evaluated, 12 groups had no unexpected results, with the VITEK®MS identification matching the reference identification. In the remaining six organism groups, the majority of the results matched the expected results. Exceptions are described below*:*

    - For the Cronobacter/Enterobacter group, there were six discrepant results in the set of 36 tests.
    - For the Enterococcus group, there was one discrepant result in the set of 21 tests.
    - For the Klebsiella/Raoultella group, there were two discrepant results in the set of 19 tests.
    - For the Moraxella group, there was one discrepant result in the set of six tests.
    - For the Morganella/Proteus group, there were three discrepant results in the set of 23 tests.
    - For the Staphylococcus group, there were four discrepant results in the set of 58 tests.

g. Sample stability studies

Sample stability studies of prepared slides were conducted using VITEK MS-DS target slides. Slides were tested at time zero and 24, 48, 72 and 96 hours after initial spotting. (Time zero means that slides were tested in the VITEK®MS directly after the spotting.) For each time tested, 48 strains (bacteria and yeast) were tested in duplicate. Prepared VITEK MS-DS target slides must be tested within 48 hours. Prepared slides should be stored at room temperature until they are tested.

h. Stability studies (reagents, slides)

Reagents - Shelf life and storage conditions:

1. VITEK MS-CHCA matrix (Ref. 411071) has a shelf-life of 365 days at 2-8^{o} C in the packaging box. The VITEK MS-CHCA matrix is stable:
    - For one week after opening and storage at 2-8 ^{o} C protected from light (in their original boxes).
    - For one week at ambient temperature (on the worktop, without protection from light) having opened the tube for up to 5 hours.

Note: The tube should be resealed after each series of CHCA matrix depositions.

2. The VITEK MS-FA (Ref. 411072) reagent has a shelf-life of 365 days at 2-8^{o} C in the packaging box. The VITEK MS-FA reagent is stable for two weeks after opening with recommended storage at 2-8 ^{o}C.

3. VITEK MS-DS target slides have a shelf life of 9 months at 15-25 ^{o} C temperature.

i. Carry-over Contamination

A study to evaluate cross contamination and carry-over was conducted with a panel of 11 strains belonging to 11 species. High positive, moderate positive and negative (matrix) samples were evaluated over multiple test runs alternating sample types. No cross contamination or carry-over was observed as all negative spots remained negative after the run.

j. Media Requirements:

VITEK®MS identification performance obtained on different media from three suppliers was evaluated. Organisms were inoculated onto different media according to their growth requirements and incubated in appropriate growth conditions. The media listed below have been validated and are included in the certificate of compatibility.

Culture Media	**bioMérieux Reference**
Columbia blood agar with 5% sheep blood	43041 / 43049
Trypticase soy agar with 5% sheep blood	43001 / 43009
Trypticase soy agar	43011 / 43019
Chocolate polyvitex agar	43101 / 43109
Campylosel agar	43361
MacConkey agar*	43141 / 43149
Modified Sabouraud dextrose agar (glucose: 20 g/l)	42066
chromID CPS	43541 / 43549

* Use of this medium from some suppliers may show less than optimal performance.

k. Culture Age:

The recommended culture incubation time for testing bacteria and yeast with the VITEK®MS organisms was generated during the building of the VITEK®MS knowledge base. Organisms were inoculated onto different media from three suppliers according to their growth requirements and incubated in appropriate conditions for 24 to 72 hours. For measurement in the VITEK®MS, bactiera and yeast growth must between 24 to 72 hours.

2. Comparison studies:

a. Method comparison with predicate device:

Not applicable. Refer to the Clinical Studies section of this document.

b. Matrix comparison:

Not applicable.

3. Clinical studies:

a. Clinical Sensitivity

Proficiency:

Prior to initiation of the clinical study, operators at each site were trained in target slide preparation, instrument use, and result review. Each operator was required to demonstrate proficiency by successfully analyzing a masked panel of organisms consisting of 10 isolates representing common aerobic and anaerobic Gram-positive and Gram-negative bacteria and yeasts.

Challenge:

A challenge study was conducted as part of the clinical trial. Three challenge panels consisting of 100 stains each were assembled; each of the panels was tested at three of the clinical trial sites.

Total Performance	Number of Isolates	Correct Identification (ID)			Discordant [1]	No Identification [2]
		Correct for Genus & Species (1 choice)	Low Discrim. (>1 choice in same genus)	Combined (1 choice + > 1 choice in same genus)		
	300	91.7% 825/900	4.4% 40/900	96.1% 865/900	0.2% 2/900	3.7% 33/900

Prospective Clinical Study:

The following performance characteristics were obtained by testing fresh strains from patient cultures, including Gram-positive bacteria, Gram- negative bacteria and yeasts, in five clinical microbiology laboratories in the United States, comparing VITEK®MS identification to a reference identification determined by molecular sequencing supplemented as needed by additional molecular sequencing and/or biochemical testing.

Organism Group	Correction Identification (ID)						
	Correct Single Choice (no. results)	Low Discrim.* Correct Genus (no. results)	Combined Correct Single Choice and Low Discrim. Correct Genus (no. results)	Single Choice Incorrect ID (no. results)[1]	Low Discrim. Incorrect Genus (no. results)	Low Discrim. Multiple Genera (no. results)	No ID[2] (no. results)
Gram-positive bacteria	89.5% (2020/2256)	4 0% (90/2256)	93 5% (2110/2256) 95% CI [92.4 ; 94 5]%	0.6% (13/2256)	0.04% (1/2256)	2.1% (48/2256)	3.7% (84/2256)
Gram-negative bacteria	83.8% (3062/3656)	9 0% (329/3656)	92 8% (3391/3656) 95% CI [91.9 ; 93 6]%	1.1% (39/3656)	0 3% (11/3656)	2 8% (104/3656)	3.0% (111/3656)
Yeasts	95.3% (1102/1156)	1 0% (11/1156)	96 3% (1113/1156) 95% CI [95.0 ; 97 3]%	0.2% (2/1156)	0 0% (0/1156)	0 6% (7/1156)	2.9% (34/1156)
Total	87.5% (6184/7068)	6.1%3 (430/7068)	93 6% (6614/7068) 95% CI [93.0 ; 94.1]%	0.8% (54/7068)	0 2% (12/7068)	2.2%4 (159/7068)	3.2% (229/7068)

Key:

1 = A table of single choice incorrect identifications is included after the Performance Characteristics by Species table.

2 = Includes No ID (i.e. Bad Spectra, Not Enough Peaks, Too Many Peaks (Bad spectrum), or No ID (Good spectrum).

3 = Of the 430 low discrimination same genus results, 426 (99.1%) had the correct species present and 4 (0.9%) did not have the correct species present.

4 = Of the 159 low discrimination multiple genera results, 140 (88.0%) had the correct species present and 19 (12.0%) did not have the correct species present.

Performance and Species Claimed in the VITEK®MS **V2.0 Knowledge Base**

Species	Number of isolates	Correct Identification (ID)			Discordant[1]	No identification[2]
		Correct for Genus & Species (1 choice)	Low Discrim. (>1 choice in same genus)	Combined (1 choice + > 1 choice in same genus)		
Abiotrophia defective	9	96.9% 31/32	0% 0/32	96.9% 31/32	0% 0/32	3.1% 1/32
Achromobacter denitrificans[3]	17	0% 0/37	91.9% 34/37	91.9% 34/37	0% 0/37	8.1% 3/37
Achromobacter xylosoxidans[3]	24	0% 0/24	91.7% 22/24	91.7% 22/24	0% 0/24	8 3% 2/24
Acinetobacter baumannii complex	65	87.9% 80/91	0% 0/91	87.9% 80/91	0% 0/91	12.1% 11/91
Acinetobacter haemolyticus	6	93.3% 28/30	3.3% 1/30	96.7% 29/30	0% 0/30	3.3% 1/30
Acinetobacter junii	11	50.0% 14/28	17.9% 5/28	67.9% 19/28	7.1% 2/28	25.0% 7/28
Acinetobacter lwoffii	26	84.6% 22/26	3.8% 1/26	88.5% 23/26	0% 0/26	11.5% 3/26
Actinomyces meyeri	8	70.0% 21/30	6.7% 2/30	76.7% 23/30	6.7% 2/30	16.7% 5/30
Actinomyces neuii	12	64.7% 33/51	0% 0/51	64.7% 33/51	2.0% 1/51	33.3% 17/51
Actinomyces odontolyticus	7	68.8% 22/32	9.4% 3/32	78.1% 25/32	0% 0/32	21.9% 7/32
Aerococcus viridans	15	97.2% 35/36	0% 0/36	97.2% 35/36	0% 0/36	2.8% 1/36
Aeromonas hydrophila/caviae [4]	25	64.0% 16/25	24.0% 6/25	88.0% 22/25	8.0% 2/25	4.0% 1/25
Aeromonas sobria [4]	10	37.9% 11/29	51.7% 15/29	89.7% 26/29	3.4% 1/29	6.9% 2/29
Aggregatibacter actinomycetemcomitans	7	83.9% 26/31	0% 0/31	83.9% 26/31	6.5% 2/31	9.7% 3/31
Aggregatibacter aphrophilus	6	83.9% 26/31	0% 0/31	83.9% 26/31	0% 0/31	16.1% 5/31
Aggregatibacter segnis	4	63.3% 19/30	6.7% 2/30	70.0% 21/30	0% 0/30	30.0% 9/30
Alcaligenes faecalis ssp faecalis	12	97.1% 33/34	0% 0/34	97.1% 33/34	2.9% 1/34	0% 0/34
Bacteroides caccae	30	95.9% 47/49	2.0% 1/49	98.0% 48/49	0% 0/49	2.0% 1/49
Bacteroides fragilis	71	98.6% 70/71	0.0% 0/71	98.6% 70/71	0% 0/71	1.4% 1/71

Performance and Species Claimed in the VITEK®MS **V2.0 Knowledge Base**

Species	Number of isolates	Correct Identification (ID)			Discordant [1]	No identification [2]
		Correct for Genus & Species (1 choice)	Low Discrim. (>1 choice in same genus)	Combined (1 choice + > 1 choice in same genus)		
Bacteroides ovatus	40	85.0% 34/40	2.5% 1/40	87.5% 35/40	0% 0/40	12.5% 5/40
Bacteroides thetaiotaomicron	51	94.1% 48/51	2.0% 1/51	96.1% 49/51	0% 0/51	3.9% 2/51
Bacteroides uniformis	30	80.4% 41/51	0% 0/51	80.4% 41/51	0% 0/51	19.6% 10/51
Bacteroides vulgatus	41	97.6% 40/41	0% 0/41	97.6% 40/41	0% 0/41	2.4% 1/41
Bordetella parapertussis	6	96.7% 29/30	3.3% 1/30	100% 30/30	0% 0/30	0% 0/30
Bordetella pertussis	9	46.7% 14/30	26.7% 8/30	73.3% 22/30	3.3% 1/30	23.3% 7/30
Brevundimonas diminuta	7	93.3% 28/30	0% 0/30	93.3% 28/30	0% 0/30	6.7% 2/30
Burkholderia multivorans	25	91.3% 42/46	4.3% 2/46	95.7% 44/46	2.2% 1/46	2.2% 1/46
Campylobacter coli	12	96.9% 31/32	0% 0/32	96.9% 31/32	3.1% 1/32	0% 0/32
Campylobacter jejuni	33	93.9% 31/33	0% 0/33	93 9% 31/33	3.0% 1/33	3.0% 1/33
Candida albicans	58	98.3% 57/58	0% 0/58	98 3% 57/58	1.7% 1/58	0% 0/58
Candida dubliniensis	34	100% 34/34	0% 0/34	100% 34/34	0% 0/34	0% 0/34
Candida famata	29	91.8% 45/49	6.1% 3/49	98.0% 48/49	0% 0/49	2.0% 1/49
Candida glabrata	62	100% 62/62	0% 0/62	100% 62/62	0% 0/62	0% 0/62
Candida guilliermondii	36	97.2% 35/36	0% 0/36	97.2% 35/36	0% 0/36	2.8% 1/36
Candida haemulonii	12	100% 34/34	0% 0/34	100% 34/34	0% 0/34	0% 0/34
Candida inconspicua	23	93.0% 40/43	2.3% 1/43	95.3% 41/43	0% 0/43	4.7% 2/43
Candida intermedia	7	92.6% 25/27	3.7% 1/27	96.3% 26/27	0% 0/27	3.7% 1/27
Candida kefyr	30	100% 30/30	0% 0/30	100% 30/30	0% 0/30	0% 0/30

Performance and Species Claimed in the VITEK®MS **V2.0 Knowledge Base**

Species	Number of isolates	Correct Identification (ID)			Discordant[1]	No identification[2]
		Correct for Genus & Species (1 choice)	Low Discrim. (>1 choice in same genus)	Combined (1 choice + > 1 choice in same genus)		
Candida krusei	53	100% 53/53	0% 0/53	100% 53/53	0% 0/53	0% 0/53
Candida lambica	9	96.8% 30/31	3.2% 1/31	100% 31/31	0% 0/31	0% 0/31
Candida lipolytica	28	100% 28/28	0% 0/28	100% 28/28	0% 0/28	0% 0/28
Candida lusitaniae	33	87.9% 29/33	3.0% 1/33	90.9% 30/33	0% 0/33	9.1% 3/33
Candida norvegensis	30	90.0% 45/50	2.0% 1/50	92.0% 46/50	0% 0/50	8.0% 4/50
Candida parapsilosis	73	98.6% 72/73	0% 0/73	98.6% 72/73	1.4% 1/73	0% 0/73
Candida pelliculosa	33	100% 33/33	0% 0/33	100% 33/33	0% 0/33	0% 0/33
Candida rugosa	6	100% 32/32	0% 0/32	100% 32/32	0% 0/32	0% 0/32
Candida tropicalis	54	90.7% 49/54	3.7% 2/54	94.4% 51/54	0% 0/54	5.6% 3/54
Candida utilis	8	96.7% 29/30	0% 0/30	96.7% 29/30	0% 0/30	3.3% 1/30
Candida zeylanoides	8	96.7% 29/30	3.3% 1/30	100% 30/30	0% 0/30	0% 0/30
Chryseobacterium indologenes	8	87.9% 29/33	0% 0/33	87.9% 29/33	0% 0/33	12.1% 4/33
Citrobacter amalonaticus	29	93.1% 27/29	3.4% 1/29	96.6% 28/29	0% 0/29	3.4% 1/29
Citrobacter braakii [5]	18	56.4% 22/39	30.8% 12/39	87 2% 34/39	5.1% 2/39	7.7% 3/39
Citrobacter freundii [5]	58	65.5% 38/58	27.6% 16/58	93.1% 54/58	6 9% 4/58	0% 0/58
Citrobacter koseri	31	100% 31/31	0% 0/31	100% 31/31	0% 0/31	0% 0/31
Citrobacter youngae [5]	13	44.1% 15/34	52 9% 18/34	97.1% 33/34	0% 0/34	2 9% 1/34
Clostridium clostridioforme	7	91.7% 11/12	0% 0/12	91.7% 11/12	8 3% 1/12	0% 0/12
Clostridium difficile	30	90.0% 27/30	0% 0/30	90.0% 27/30	0% 0/30	10.0% 3/30

Performance and Species Claimed in the VITEK®MS **V2.0 Knowledge Base**

Species	Number of isolates	Correct Identification (ID)			Discordant[1]	No identification[2]
		Correct for Genus & Species (1 choice)	Low Discrim. (>1 choice in same genus)	Combined (1 choice + > 1 choice in same genus)		
Clostridium perfringens	61	98.4% 60/61	0% 0/61	98.4% 60/61	0% 0/61	1.6% 1/61
Clostridium ramosum	10	90.3% 28/31	0% 0/31	90.3% 28/31	3.2% 1/31	6.5% 2/31
Corynebacterium jeikeium	8	100% 31/31	0% 0/31	100% 31/31	0% 0/31	0% 0/31
Cronobacter sakazakii	10	73.3% 22/30	26.7% 8/30	100% 30/30	0% 0/30	0% 0/30
Cryptococcus neoformans	35	100% 35/35	0% 0/35	100% 35/35	0% 0/35	0% 0/35
Edwardsiella hoshinae	11	93.9% 31/33	6.1% 2/33	100% 33/33	0% 0/33	0% 0/33
Edwardsiella tarda	9	93.1% 27/29	6 9% 2/29	100% 29/29	0% 0/29	0% 0/29
Eikenella corrodens	14	100% 34/34	0% 0/34	100% 34/34	0% 0/34	0% 0/34
Elizabethkingia meningoseptica	10	100% 32/32	0% 0/32	100% 32/32	0% 0/32	0% 0/32
Enterobacter aerogenes	52	100% 52/52	0% 0/52	100% 52/52	0% 0/52	0% 0/52
Enterobacter asburiae [6]	12	0% 0/33	87 9% 29/33	87.9% 29/33	0% 0/33	12.1% 4/33
Enterobacter cancerogenus	6	61.3% 19/31	29.0% 9/31	90.3% 28/31	3.2% 1/31	6 5% 2/31
Enterobacter cloacae [6]	28	0% 0/28	92.9% 26/28	92.9% 26/28	3.6% 1/28	3.6% 1/28
Enterobacter gergoviae	10	90.6% 29/32	0% 0/32	90.6% 29/32	3.1% 1/32	6 3% 2/32
Enterococcus avium	33	90.9% 30/33	3.0% 1/33	93 9% 31/33	0% 0/33	6.1% 2/33
Enterococcus casseliflavus	37	100% 37/37	0% 0/37	100% 37/37	0% 0/37	0% 0/37
Enterococcus durans	30	96.7% 29/30	0% 0/30	96.7% 29/30	3.3% 1/30	0% 0/30
Enterococcus faecalis	68	97.1% 66/68	0% 0/68	97.1% 66/68	0% 0/68	2 9% 2/68
Enterococcus faecium	57	100% 57/57	0% 0/57	100% 57/57	0% 0/57	0% 0/57

Performance and Species Claimed in the VITEK®MS **V2.0 Knowledge Base**

Species	Number of isolates	Correct Identification (ID)			Discordant[1]	No identification[2]
		Correct for Genus & Species (1 choice)	Low Discrim. (>1 choice in same genus)	Combined (1 choice + > 1 choice in same genus)		
Enterococcus gallinarum	34	100% 34/34	0% 0/34	100% 34/34	0% 0/34	0% 0/34
Escherichia coli [7]	65	100% 65/65	0% 0/65	100% 65/65	0% 0/65	0% 0/65
Escherichia fergusonii	6	48.1% 13/27	22.2% 6/27	70.4% 19/27	7.4% 2/27	22.2% 6/27
Escherichia hermannii	7	78.1% 25/32	0% 0/32	78.1% 25/32	3.1% 1/32	18.8% 6/32
Ewingella americana	6	90.0% 27/30	0% 0/30	90.0% 27/30	3.3% 1/30	6.7% 2/30
Finegoldia magna	24	97.7% 43/44	0% 0/44	97.7% 43/44	0% 0/44	2.3% 1/44
Fusobacterium necrophorum	26	88.9% 40/45	0% 0/45	88.9% 40/45	0% 0/45	11.1% 5/45
Fusobacterium nucleatum	7	59.1% 13/22	4 5% 1/22	63.6% 14/22	9.1% 2/22	27.3% 6/22
Gardnerella vaginalis	27	88.4% 38/43	0% 0/43	88.4% 38/43	0% 0/43	11.6% 5/43
Gemella haemolysans	11	78.8% 26/33	18 2% 6/33	97.0% 32/33	0% 0/33	3.0% 1/33
Gemella morbillorum	5	46.7% 14/30	40.0% 12/30	86.7% 26/30	0% 0/30	13.3% 4/30
Geotrichum capitatum	32	93.8% 30/32	0% 0/32	93.8% 30/32	0% 0/32	6.3% 2/32
Granulicatella adiacens	6	100% 31/31	0% 0/31	100% 31/31	0% 0/31	0% 0/31
Haemophilus influenzae	55	96.4% 53/55	0% 0/55	96.4% 53/55	0% 0/55	3.6% 2/55
Haemophilus parahaemolyticus	8	100% 31/31	0% 0/31	100% 31/31	0% 0/31	0% 0/31
Haemophilus parainfluenzae	37	91.9% 34/37	2.7% 1/37	94.6% 35/37	0% 0/37	5.4% 2/37
Hafnia alvei	19	84.2% 16/19	0% 0/19	84.2% 16/19	5.3% 1/19	10.5% 2/19
Kingella denitrificans	3	95.8% 23/24	0% 0/24	95.8% 23/24	0% 0/24	4.2% 1/24
Kingella kingae	4	83.3% 25/30	0% 0/30	83.3% 25/30	0% 0/30	16.7% 5/30

Performance and Species Claimed in the VITEK®MS **V2.0 Knowledge Base**

Species	Number of isolates	Correct Identification (ID)			Discordant[1]	No identification[2]
		Correct for Genus & Species (1 choice)	Low Discrim. (>1 choice in same genus)	Combined (1 choice + > 1 choice in same genus)		
Klebsiella oxytoca	49	100% 49/49	0% 0/49	100% 49/49	0% 0/49	0% 0/49
Klebsiella pneumoniae	58	100% 58/58	0% 0/58	100% 58/58	0% 0/58	0% 0/58
Kodamaea ohmeri	11	93.5% 29/31	0% 0/31	93.5% 29/31	0% 0/31	6.5% 2/31
Lactococcus garvieae	9	100% 31/31	0% 0/31	100% 31/31	0% 0/31	0% 0/31
Lactococcus lactis ssp lactis	10	93.5% 29/31	3.2% 1/31	96.8% 30/31	0% 0/31	3.2% 1/31
Leclercia adecarboxylata	10	93.5% 29/31	0% 0/31	93 5% 29/31	0% 0/31	6.5% 2/31
Legionella pneumophila	26	96.1% 49/51	0% 0/51	96.1% 49/51	0% 0/51	3.9% 2/51
Leuconostoc mesenteroides	11	93.5% 29/31	0% 0/31	93.5% 29/31	0% 0/31	6.5% 2/31
Leuconostoc pseudomesenteroides	5	76.0% 19/25	0% 0/25	76.0% 19/25	0% 0/25	24.0% 6/25
Listeria monocytogenes	45	75.6% 34/45	8 9% 4/45	84.4% 38/45	0% 0/45	15.6% 7/45
Malassezia furfur	7	94.6% 35/37	0% 0/37	94.6% 35/37	0% 0/37	5.4% 2/37
Malassezia pachydermatis	8	46.4% 13/28	0% 0/28	46.4% 13/28	0% 0/28	53.6% 15/28
Micrococcus luteus/lylae	35	94.3% 33/35	0% 0/35	94 3% 33/35	0% 0/35	5.7% 2/35
Mobiluncus curtisii	4	86.2% 25/29	0% 0/29	86 2% 25/29	0% 0/29	13.8% 4/29
Moraxella (Branhamella) catarrhalis	33	100% 33/33	0% 0/33	100% 33/33	0% 0/33	0% 0/33
Morganella morganii	52	100% 52/52	0% 0/52	100% 52/52	0% 0/52	0% 0/52
Neisseria cinerea	9	90.6% 29/32	3.1% 1/32	93.8% 30/32	0% 0/32	6.3% 2/32
Neisseria gonorrhoeae [8]	29	89.7% 26/29	3.4% 1/29	93.1% 27/29	0% 0/29	6.9% 2/29
Neisseria meningitidis	9	96.9% 31/32	0% 0/32	96 9% 31/32	0% 0/32	3.1% 1/32

Performance and Species Claimed in the VITEK®MS **V2.0 Knowledge Base**

Species	Number of isolates	Correct Identification (ID)			Discordant[1]	No identification[2]
		Correct for Genus & Species (1 choice)	Low Discrim. (>1 choice in same genus)	Combined (1 choice + > 1 choice in same genus)		
Neisseria mucosa	9	63.3% 19/30	23 3% 7/30	86.7% 26/30	0% 0/30	13.3% 4/30
Ochrobactrum anthropi	10	90.3% 28/31	0% 0/31	90 3% 28/31	3.2% 1/31	6.5% 2/31
Oligella ureolytica	9	86.7% 26/30	0% 0/30	86.7% 26/30	0% 0/30	13.3% 4/30
Oligella urethralis	14	88.2% 30/34	0% 0/34	88 2% 30/34	2.9% 1/34	8.8% 3/34
Pantoea agglomerans	22	86.4% 19/22	0% 0/22	86.4% 19/22	13.6% 3/22	0% 0/22
Parvimonas micra	10	85.3% 29/34	0% 0/34	85.3% 29/34	0% 0/34	14.7% 5/34
Pasteurella multocida	14	100% 36/36	0% 0/36	100% 36/36	0% 0/36	0% 0/36
Pediococcus acidilactici	7	92.6% 25/27	0% 0/27	92.6% 25/27	0% 0/27	7.4% 2/27
Peptoniphilus asaccharolyticus	4	100% 14/14	0% 0/14	100% 14/14	0% 0/14	0% 0/14
Peptostreptococcus anaerobius	36	94.6% 53/56	0% 0/56	94.6% 53/56	1.8% 1/56	3.6% 2/56
Prevotella bivia	34	100.0% 34/34	0% 0/34	100% 34/34	0% 0/34	0% 0/34
Prevotella buccae	23	93.8% 45/48	0% 0/48	93.8% 45/48	0% 0/48	6.3% 3/48
Prevotella denticola	6	93.5% 29/31	0% 0/31	93.5% 29/31	0% 0/31	6.5% 2/31
Prevotella intermedia	16	85.2% 23/27	3.7% 1/27	88.9% 24/27	0% 0/27	11.1% 3/27
Prevotella melaninogenica	11	61.5% 16/26	7.7% 2/26	69.2% 18/26	7.7% 2/26	23.1% 6/26
Propionibacterium acnes	52	82.7% 43/52	1 9% 1/52	84.6% 44/52	0% 0/52	15.4% 8/52
Proteus mirabilis	58	98.3% 57/58	0% 0/58	98 3% 57/58	0% 0/58	1.7% 1/58
Proteus penneri [9]	19	0% 0/39	97.4% 38/39	97.4% 38/39	0% 0/39	2.6% 1/39
Proteus vulgaris [9]	23	0% 0/23	100% 23/23	100% 23/23	0% 0/23	0% 0/23

Performance and Species Claimed in the VITEK®MS **V2.0 Knowledge Base**

Species	Number of isolates	Correct Identification (ID)			Discordant[1]	No identification[2]
		Correct for Genus & Species (1 choice)	Low Discrim. (>1 choice in same genus)	Combined (1 choice + > 1 choice in same genus)		
Providencia rettgeri	33	97.0% 32/33	0% 0/33	97.0% 32/33	0% 0/33	3.0% 1/33
Providencia stuartii	31	100% 31/31	0% 0/31	100% 31/31	0% 0/31	0% 0/31
Pseudomonas aeruginosa	57	96.5% 55/57	0% 0/57	96 5% 55/57	0% 0/57	3.5% 2/57
Pseudomonas fluorescens	19	78.9% 15/19	15.8% 3/19	94.7% 18/19	0% 0/19	5.3% 1/19
Pseudomonas putida	25	80.0% 20/25	4.0% 1/25	84.0% 21/25	4.0% 1/25	12.0% 3/25
Pseudomonas stutzeri	8	87.9% 29/33	0% 0/33	87 9% 29/33	6.1% 2/33	6.1% 2/33
Ralstonia pickettii	10	70.4% 19/27	0% 0/27	70.4% 19/27	3.7% 1/27	25.9% 7/27
Raoultella ornithinolytica	11	90.6% 29/32	3.1% 1/32	93.8% 30/32	3.1% 1/32	3.1% 1/32
Raoultella planticola	9	80.6% 25/31	0% 0/31	80.6% 25/31	3 2% 1/31	16.1% 5/31
Rhizobium radiobacter	14	81.8% 27/33	0% 0/33	81.8% 27/33	9.1% 3/33	9.1% 3/33
Rhodotorula mucilaginosa	35	100% 35/35	0% 0/35	100% 35/35	0% 0/35	0% 0/35
Rothia mucilaginosa	8	50.0% 16/32	3.1% 1/32	53.1% 17/32	0% 0/32	46.9% 15/32
Saccharomyces cerevisiae	42	97.6% 41/42	0% 0/42	97.6% 41/42	0% 0/42	2.4% 1/42
Salmonella group [8]	35	94.3% 33/35	5.7% 2/35	100% 35/35	0% 0/35	0% 0/35
Serratia fonticola	7	66.7% 20/30	23 3% 7/30	90.0% 27/30	3.3% 1/30	6.7% 2/30
Serratia liquefaciens	23	95.7% 22/23	4 3% 1/23	100% 23/23	0% 0/23	0% 0/23
Serratia marcescens	57	100% 57/57	0% 0/57	100% 57/57	0% 0/57	0% 0/57
Serratia odorifera	30	100% 30/30	0% 0/30	100% 30/30	0% 0/30	0% 0/30
Sphingobacterium multivorum	5	86.2% 25/29	0% 0/29	86.2% 25/29	3.4% 1/29	10.3% 3/29

Performance and Species Claimed in the VITEK®MS **V2.0 Knowledge Base**

Species	Number of isolates	Correct Identification (ID)			Discordant[1]	No identification[2]
		Correct for Genus & Species (1 choice)	Low Discrim. (>1 choice in same genus)	Combined (1 choice + > 1 choice in same genus)		
Sphingobacterium spiritivorum	10	96.7% 29/30	0% 0/30	96.7% 29/30	3.3% 1/30	0% 0/30
Sphingomonas paucimobilis	9	96.8% 30/31	0% 0/31	96.8% 30/31	0% 0/31	3.2% 1/31
Staphylococcus aureus	61	98.4% 60/61	0% 0/61	98.4% 60/61	0% 0/61	1.6% 1/61
Staphylococcus capitis	34	94.1% 32/34	0% 0/34	94.1% 32/34	2.9% 1/34	2.9% 1/34
Staphylococcus cohnii ssp cohnii	8	93.3% 28/30	6.7% 2/30	100% 30/30	0% 0/30	0% 0/30
Staphylococcus cohnii ssp urealyticus	12	96.8% 30/31	0% 0/31	96.8% 30/31	0% 0/31	3.2% 1/31
Staphylococcus epidermidis	88	97.7% 86/88	0% 0/88	97.7% 86/88	2.3% 2/88	0% 0/88
Staphylococcus haemolyticus	38	100% 38/38	0% 0/38	100% 38/38	0% 0/38	0% 0/38
Staphylococcus hominis ssp hominis	21	100% 21/21	0% 0/21	100% 21/21	0% 0/21	0% 0/21
Staphylococcus lugdunensis	33	100% 33/33	0% 0/33	100% 33/33	0% 0/33	0% 0/33
Staphylococcus saprophyticus	35	91.4% 32/35	0% 0/35	91.4% 32/35	0% 0/35	8.6% 3/35
Staphylococcus schleiferi	7	100% 32/32	0% 0/32	100% 32/32	0% 0/32	0% 0/32
Staphylococcus sciuri	7	93.3% 28/30	3.3% 1/30	96.7% 29/30	0% 0/30	3.3% 1/30
Staphylococcus simulans	31	100% 31/31	0% 0/31	100% 31/31	0% 0/31	0% 0/31
Staphylococcus warneri	33	84.8% 28/33	0% 0/33	84.8% 28/33	3.0% 1/33	12.1% 4/33
Stenotrophomonas maltophilia	53	96.2% 51/53	0% 0/53	96 2% 51/53	1.9% 1/53	1.9% 1/53
Streptococcus agalactiae	58	100% 58/58	0% 0/58	100% 58/58	0% 0/58	0% 0/58
Streptococcus anginosus	47	95.7% 45/47	0% 0/47	95.7% 45/47	0% 0/47	4.3% 2/47
Streptococcus constellatus	30	86.7% 26/30	6.7% 2/30	93 3% 28/30	0% 0/30	6.7% 2/30

Performance and Species Claimed in the VITEK®MS **V2.0 Knowledge Base**

Species	Number of isolates	Correct Identification (ID)			Discordant[1]	No identification[2]
		Correct for Genus & Species (1 choice)	Low Discrim. (>1 choice in same genus)	Combined (1 choice + > 1 choice in same genus)		
Streptococcus dysgalactiae ssp equisimilis/Streptococcus dysgalactiae ssp dysgalactiae	47	0% 0/47	93.6% 44/47	93.6% 44/47	0% 0/47	6.4% 3/47
Streptococcus gallolyticus ssp gallolyticus	5	100% 30/30	0% 0/30	100% 30/30	0% 0/30	0% 0/30
Streptococcus infantarius ssp coli (Str.lutetiensis)	9	100% 31/31	0% 0/31	100% 31/31	0% 0/31	0% 0/31
Streptococcus infantarius ssp infantarius	12	94.1% 32/34	2 9% 1/34	97.1% 33/34	0% 0/34	2.9% 1/34
Streptococcus intermedius	20	88.4% 38/43	11.6% 5/43	100% 43/43	0% 0/43	0% 0/43
Streptococcus mitis/Streptococcus oralis	37	86.5% 32/37	2.7% 1/37	89.2% 33/37	0% 0/37	10.8% 4/37
Streptococcus mutans	9	87.1% 27/31	6 5% 2/31	93.5% 29/31	0% 0/31	6.5% 2/31
Streptococcus pneumoniae	51	96.1% 49/51	0% 0/51	96.1% 49/51	0% 0/51	3.9% 2/51
Streptococcus pyogenes	55	96.4% 53/55	0% 0/55	96.4% 53/55	0% 0/55	3.6% 2/55
Streptococcus salivarius ssp salivarius	8	93.8% 30/32	3.1% 1/32	96 9% 31/32	0% 0/32	3.1% 1/32
Streptococcus sanguinis	34	91.2% 31/34	0% 0/34	91.2% 31/34	8.8% 3/34	0.0% 0/34
Trichosporon asahii	32	93.8% 30/32	0% 0/32	93.8% 30/32	0% 0/32	6.3% 2/32
Trichosporon inkin	9	100% 30/30	0% 0/30	100% 30/30	0% 0/30	0% 0/30
Trichosporon mucoides	9	97.1% 33/34	0% 0/34	97.1% 33/34	0% 0/34	2.9% 1/34
Vibrio cholerae	11	90.9% 30/33	3.0% 1/33	93.9% 31/33	3.0% 1/33	3.0% 1/33
Vibrio parahaemolyticus	16	94.4% 34/36	2.8% 1/36	97.2% 35/36	0% 0/36	2.8% 1/36
Vibrio vulnificus	11	93.9% 31/33	0% 0/33	93.9% 31/33	0% 0/33	6.1% 2/33
Yersinia enterocolitica	14	100% 35/35	0% 0/35	100% 35/35	0% 0/35	0% 0/35

Performance and Species Claimed in the VITEK®MS **V2.0 Knowledge Base**

Species	Number of isolates	Correct Identification (ID)			Discordant[1]	No identification[2]
		Correct for Genus & Species (1 choice)	Low Discrim. (>1 choice in same genus)	Combined (1 choice + > 1 choice in same genus)		
Yersinia frederiksenii	10	80.0% 24/30	6.7% 2/30	86.7% 26/30	3.3% 1/30	10.0% 3/30
Yersinia intermedia	9	90.0% 27/30	10.0% 3/30	100% 30/30	0% 0/30	0% 0/30
Yersinia kristensenii	7	90.0% 27/30	6.7% 2/30	96.7% 29/30	0% 0/30	3.3% 1/30
Yersinia pseudotuberculosis	8	96.7% 29/30	3 3% 1/30	100% 30/30	0% 0/30	0% 0/30

*Discrim. = Discrimination

1 = Includes single choice incorrect identifications and low discrimination results with >1 choice in same genus but genus does not match the reference genus.

2 = Includes Low Discrimination with multiple genera or No ID (i.e. Bad Spectra, Not Enough Peaks, Too Many Peaks (Bad spectrum), or No ID (Good spectrum).

3 = *Achromobacter denitrificans* and *Achromobacter xylosoxidans* identifications should be considered as a slashline result, *Achromobacter denitrificans/ Achromobacter xylosoxidans*.

4 = *Aeromonas hydrophila/caviae* and *Aeromonas sobria* should be considered as an *Aeromonas* species group identification.

5 = *Citrobacter freundii*, *Citrobacter braakii* and *Citrobacter youngae* should be considered as *Citrobacter freundii* complex.

6 = *Enterobacter cloacae* and *Enterobacter asburiae* identifications should be considered as a slashline result, *Enterobacter cloacae/ Enterobacter asburiae*.

7 = Shigella species and *E. coli* O157 are identified as *Escherichia coli*. Confirmatory tests are required to differentiate *Escherichia coli* from *Shigella* species or *E. coli* O157.

8 = Confirmatory tests are recommended for *Neisseria gonorrhoeae*; Salmonella: confirm by serological tests.

9 = *Proteus penneri* and *Proteus vulgaris* identifications should be considered as a slashline result, *Proteus penneri/ Proteus vulgaris*.

Single Choice Discordant Results

No.	*Reference Result*	*VITEK® MS Result*
2	*Acinetobacter junii*	*Acinetobacter haemolyticus*
2	*Actinomyces meyeri*	*Actinomyces odontolyticus*
1	*Actinomyces neuii ssp neuii*	*Bacteroides vulgatus*
2	*Aeromonas caviae*	*Aeromonas sobria*
1	*Aeromonas sobria*	*Aggregatibacter hydrophila/caviae*
1	*Aggregatibacter actinomycetemcomitans*	*Aggregatibacter aphrophilus*
1	*Aggregatibacter actinomycetemcomitans*	*Sphingobacterium spiritivorum*
1	*Alcaligenes faecalis ssp faecalis*	*Staphylocccus aureus*
1	*Bordetella pertussis*	*Bordetella parapertussis*
1	*Burkholderia multivorans*	*Yersinia ruckeri**
1	*Campylobacter coli*	*Campylobacter jejuni*
1	*Campylobacter jejuni*	*Campylobacter coli*
1	*Candida albicans*	*Candida dubliniensis*
1	*Candida parapsilosis*	*Candida pelliculosa*
1	*Citrobacter braakii*	*Citrobacter freundii*
1	*Citrobacter braakii*	*Citrobacter youngae*
2	*Citrobacter freundii*	*Citrobacfter werkmanii*
2	*Citrobacter freundii*	*Citrobacter youngae*
1	*Clostridium clostridioforme*	*Clostridium bifermentans**
1	*Clostridium ramosum*	*Propionibacterium propionicum*
1	*Enterobacter cancerogenus*	*Klebsiella oxytoca*
1	*Enterobacter gergoviae*	*Enterobacter aerogenes*
1	*Enterococcus durans*	*Enterococcus faecium*

No.	*Reference Result*	*VITEK® MS Result*
2	*Escherichia fergusonii*	*Escherichia coli*
1	*Escherichia hermannii*	*Citrobacter koseri*
1	*Ewingella americana*	*Enterobacter gergoviae*
1	*Hafnia alvei*	*Obesumbacterium proteus**
1	*Ochrobactrum anthropi*	*Corynebacterium striatum**
2	*Pantoea agglomerans*	*Enterobacter cancerogenus*
1	*Peptostreptococcus anaerobius*	*Clostridium sordellii**
1	*Prevotella melaninogenica*	*Micrococcus luteus/lylae*
1	*Pseudomonas putida*	*Pseudomonas viridiflava**
1	*Pseudomonas stutzeri*	*Moraxella (Branhamella) catarrhalis*
1	*Raoultella ornithinolytica*	*Enterboacter aerogenes*
1	*Raoultella planticola*	*Raoultella ornithinolytica*
1	*Rhizobium radiobacter*	*Obesumbacterium proteus**
1	*Serratia fonticola*	*Serratia liquefaciens*
1	*Sphingobacterium multivorum*	*Myroides spp**
1	*Staphylococcus epidermidis*	*Staphylococcus hominis* ssp *hominis*
1	*Staphylococcus epidermidis*	*Staphylococcus caprae**
1	*Staphylococcus warneri*	*Staphylococcus pasteuri**
1	*Streptococcus maltophilia*	*Ochrobactrum anthropi*
2	*Streptococcus sanguinis*	*Streptococcus mitis/oralis*
1	*Streptococcus sanguinis*	*Streptococcus anginosus*
1	*Vibrio cholerae*	*Vibrio parahaemolyticus*
1	*Yersinia frederiksenii*	*Yersinia pseudotuberculosis*

* This VITEK®MS identification indicates that the VITEK®MS result is a non-clinically validated organism. These organisms are displayed in the VITEK®MS report as a means of directing additional laboratory testing. Identification of non-clinically validated organisms must be performed with an alternate laboratory method.

Non-clinically validated organisms include:

- Organisms with insufficient clinical performance data.
- Organisms not found in human clinical samples as reported in the scientific literature.

Results for non-clinically validated organisms cannot be transmitted from the VITEK®MS to the LIS.

M. Instrument Names:

VITEK®MS

N. System Description:

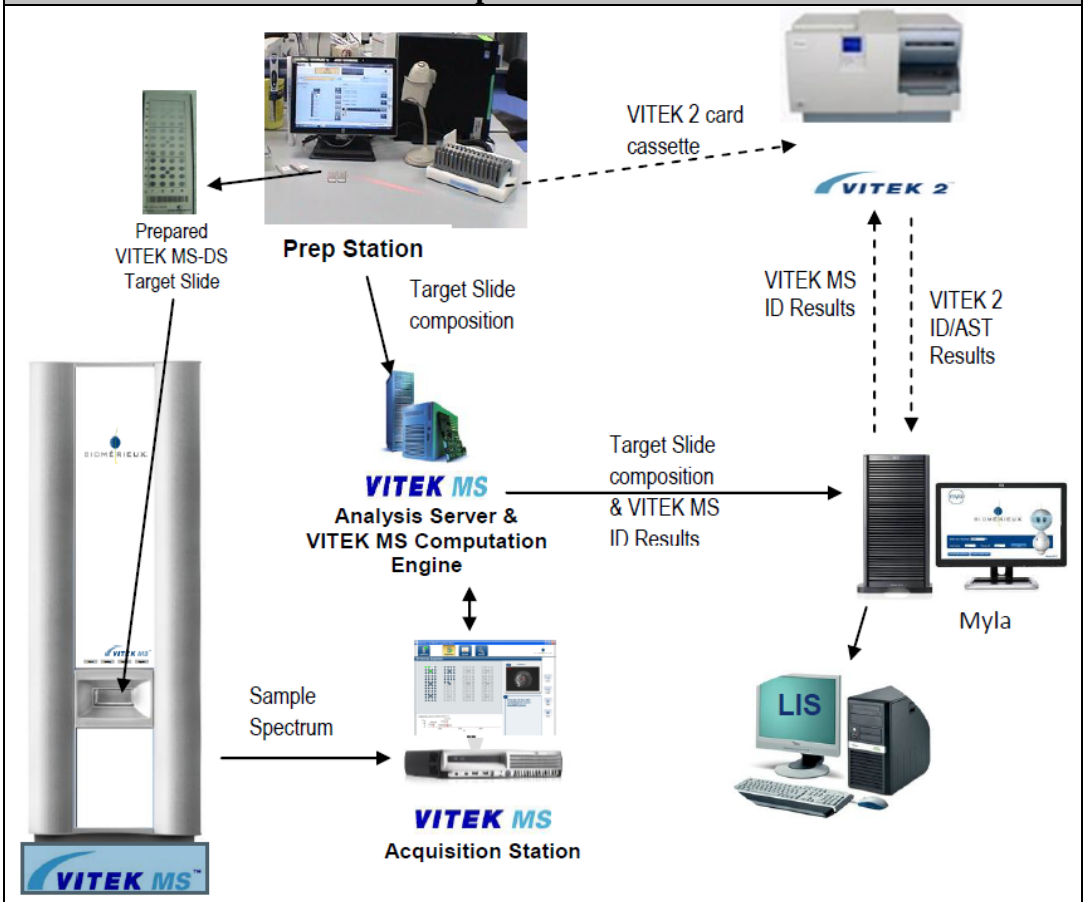
1. <u>Modes of Operation</u>:

The VITEK®MS system is based on a matrix-assisted laser desorption ionization-time of flight mass spectrometer (MALDI-TOF MS). The VITEK®MS analyzes material from microbial cultures to provide organism identification. Microbial specimens are analyzed based on the dynamics of particles ionized by a laser shot in a vacuum tube. The resulting spectrum of mass distribution is interpreted according to an algorithm developed by the Firm.

A portion of a microbial colony from an agar plate is applied to a spot on a VITEK MS-DS target slide. A matrix solution is applied to the spot. The target slide is dried and then loaded into the VITEK® MS instrument. The sample is exposed to multiple laser shots, the matrix absorbs the laser light and vaporizes along with the sample and in the process the sample gains an electrical charge (ionization). Electric fields accelerate and guide the ions into the vacuum tube which separates them according to mass as the smaller molecules fly faster than the larger ones. At the end of the flight path there is a detector which records the number of ions striking it per unit time. The intensity data from the detector is displayed as a function of the time of flight and the result is a series of peaks which correspond to different molecular fragments of sample each having a unique mass to charge ratio. Each unique organism will produce a unique and repeatable mass spectrum. The resulting spectrum of mass distribution will be interpreted by comparing with a to previously acquired known spectral database developed by the Firm to provide organism identification results with a confidence level.

An overview of the workflow is presented in the graphic below along with a table describing the function of each system component. After the colony is chosen and placed on the Target Slide with matrix, all other analysis steps are performed by the VITEK®MS.

Overview of the VITEK MS Components



Workflow step	Target slide	Output Data
Sample Preparation	VITEK MS-DS target slides are prepared	The VITEK MS-DS target slide and sample barcodes are read on the VITEK® MS Prep Station to identify the spots on the VITEK MS-DS target slides Target slide data are sent to VITEK® MS Prep and Myla ™.
Verify VITEK MS-DS target slide composition		The VITEK MS-DS target slide description screen is displayed in Myla ™.
Start Analysis	Target slides are placed on the adapter, the adapter is then loaded into the VITEK® MS instrument and the analysis is started.	The VITEK MS-DS target slide barcodes are read on the VITEK® MS Prep Acquisition Station to indicate the order in which they are processed by the VITEK®MS.
Review Identification results		The VITEK® MS Prep identification results are consolidated (if necessary), displayed and reviewed in Myla ™. The reviewed results are sent by Myla ™ to the LIS if the one-step review process is selected.
Approve consolidated Identification results and the corresponding data entry		If the two-step 'Review and Approve for result Validation' setting is enabled in Myla™, the VITEK® MS Prep identification results previously reviewed can then be approved on Myla™ then sent to the LIS.

2. Software:

FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:
Yes ___X____ or No _____

Level of Concern:

Moderate

Software Description:

VITEK®MS Acquisition Station
The VITEK MS Acquisition Station consists of a computer equipped with a barcode reader. It is connected to the VITEK®MS instrument via USB, serial and camera ports. The VITEK MS Acquisition Station receives prepared VITEK MS-DS data from the VITEK MS Analysis Server software and acquisition results from the VITEK®MS instrument. It displays the spectra and peak lists and transfers the peak lists to the VITEK MS Analysis Server.

VITEK®MS Prep Station
The VITEK® MS Prep Station consists of a computer equipped with a barcode reader and the VITEK MS Prep Station Hardware. The VITEK® MS Prep Station is used to prepare VITEK MS-DS target slides and to enter VITEK MS-DS slide data into the system software. The VITEK MS slide data are transferred from the VITEK MS Prep Station to the VITEK® MS Analysis Server software which resides within the Myla™ server PC. The VITE® MS Prep Station Hardware is connected via USB to the VITEK® MS Prep Station. It is used to record data on the cassette memory chip: sample ID and card data.

Myla™
Myla™ is a computer application ("Middleware"), based on Web technology. Myla™ interfaces with a number of the Firms analytical instruments connected to the application and the LIS (Laboratory Information System). Myla™ displays information related to the laboratory workflow and the following functions:

- Displays system information.
- Displays ID results from the VITEK®MS
- Displays the sample positions on the slide for the VITEK®MS
- Enables VITEK®MS identification results to be sent to the VITEK 2 and/or the LIS, depending on the result validation workflow selected
- The computer (server) which hosts the Myla™ application also hosts the VITEK® MS Analysis Server that manages the VITEK®MS workflow and the Computation Engine. The VITEK ®MS analysis server sends the acquired data to the computation engine that calculates the identification results. The algorithms and mapping files required for identification are contained within the computation engine.

Device Hazard Analysis:

The Risk Management Report documents the results of verification, evaluates the residual risk, and determines whether the benefit of the device outweighs any residual risks. Sections 4.1.12, 4.2.9, and 11.9 contain the Risk Management Plan and Safety Risk Management File, documenting the VITEK®MS, Myla™, and VITEK®MS Plus hazard analysis, respectively.

The Risk Management Plan describes the strategy followed to analyze and manage the risks at the system level and at the sub-systems/components level knowing that it is a continuous process followed during the development cycle and updated as long as the product is on the market. At the system level, the risk analysis is used to identify:

- The potential hazards linked to the life cycle of the product (from design/manufacturing to product withdrawal). The preliminary requirements document and the system requirements will serve as a basis. The hazards considered include those related to people (patients, consumers, users or third party), property and environment.
- The part of the system that will be involved in the hazard cause or mitigation. The system shall be seen as an assembly of subsystems (disposables, instrument, user interface software) that interact between themselves, and with external stakeholders (users and LIS). Subsystems are viewed as black boxes and risks linked to the interface have to be identified at this stage.

The objective of the risk management activities is to deliver a risk analysis report, which contains:

- Device characteristics that could impact safety [ISO 14971]
- Software safety classification [IEC 62304]
- Risk analysis table
- Risk traceability matrix with design requirements
- Overall assessment of residual risk

The risk analysis is organized into the following categories:

- System risk analysis
- Instrument risk analysis
- Software risk analysis
- Matrix risk analysis
- CLSI Auto 11A considerations
- Connectivity risk assessment

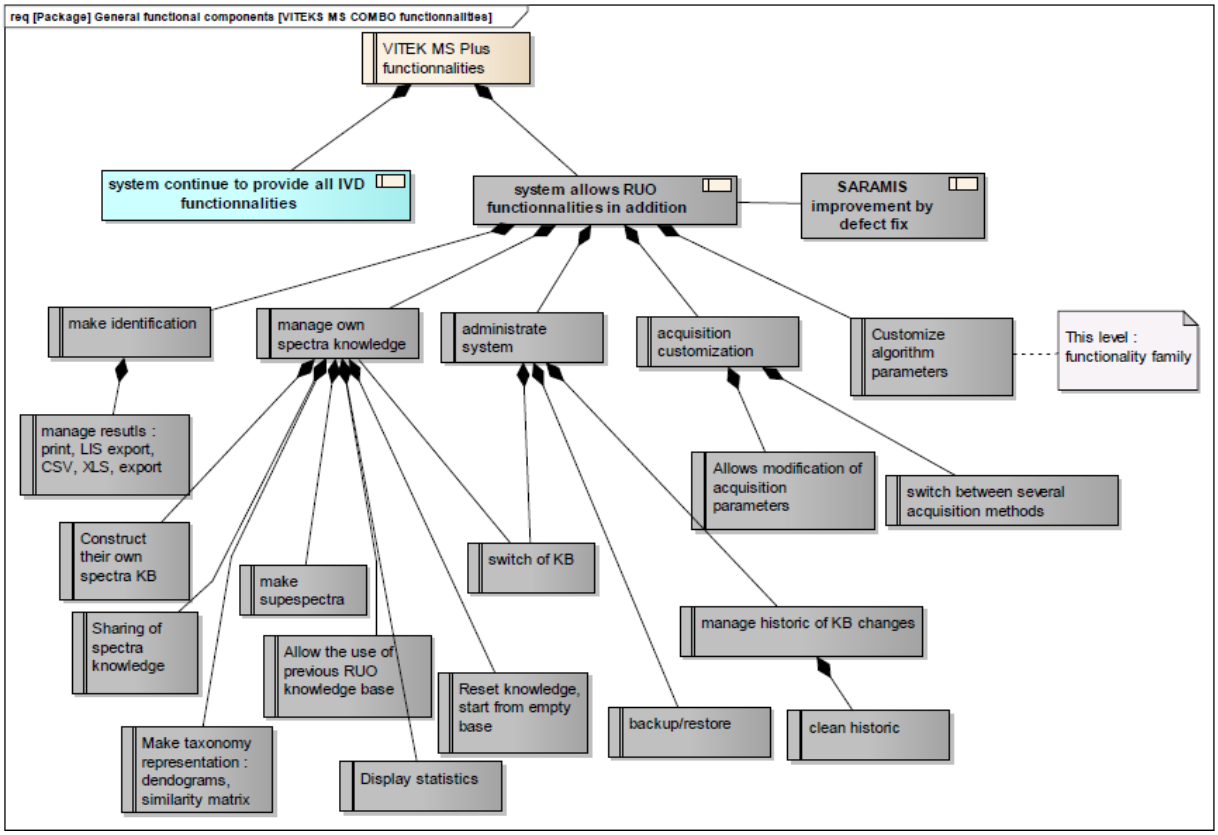
At the sub-system/component level the approach is a bottom-up analysis based upon FMEA and on the hazards already identified at the system level. The sub-system/component detailed risk analysis includes the risks that have been identified at the system level as long as the given sub-system is involved in the risk mitigation or in the cause. Specific risks identified inside each sub-system/component were acceptably addressed. At the end of the process the final system risk was re-assessed based upon the verification and validation of the risk mitigation actions.

The Risk Analysis report identified the causes of all potential hazards associated with the device and the controls that have been developed to mitigate such risks. A remaining residual hazard identified during the final risk analysis and validation testing of the instrument control software showed that the user is able to swap slide bar codes during reading, references to proper workflow and how to scan bar codes are mentioned in the user manual in order to prevent the inaccurate

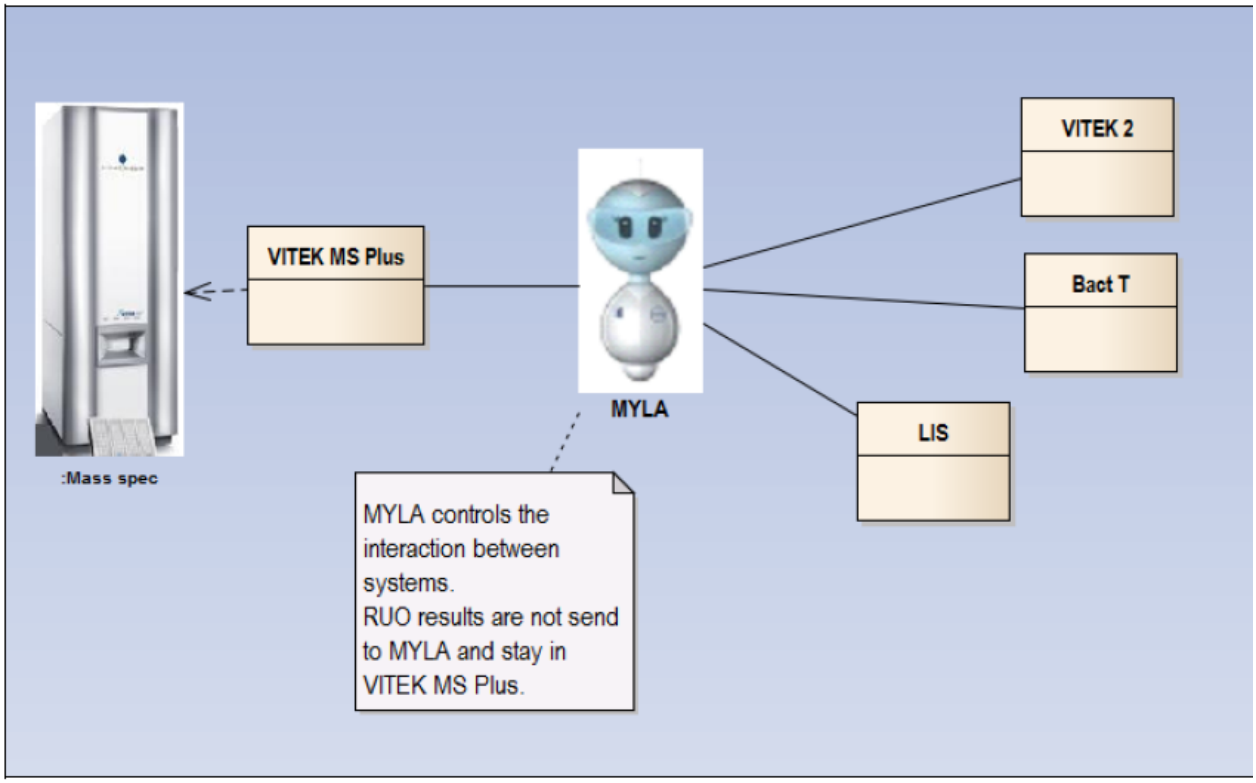
results that cause inappropriate physician action. All other hazards have been successfully mitigated to an acceptable level, and no new additional hazards have been identified.

Architecture Design Chart:

The following graphic shows the architectural layout and relationships of all components which make up the VITEK®MS software.



The IVD components of the VITEK ®MS COMBO system, as part of a product linked with Myla™ have interactions with the other Firm manufactured products compatible with Myla™. For example, in the same lab, the VITEK 2 system or the BacT/ALERT system could be added and interconnected with the VITEK ®MS COMBO via Myla™ middleware. These systems can share resources such as: ViLink, BCILink, IVD results common management (like result validation, report generation) in the Myla™ interface. RUO results that are generated by SARAMIS do not have interactions with Myla™ and do not have any in interactions with other bioMérieux systems. Below is a simplified graphic showing the star type communication model Myla™ implements to communicate and control other systems compatible with the interface.


VITEK 2
VITEK MS Plus
Bact T
MYLA
LIS
:Mass spec
MYLA controls the interaction between systems.
RUO results are not send to MYLA and stay in VITEK MS Plus.

1.0 SOFTWARE DEVELOPMENT ENVIRONMENT

The Myla™ V3.0.0 software was developed following an iterative mode, before entering into formal verification and validation.

The software project life cycle consists of following three phases.

- Design phase
- Implementation phase
- Verification phase

The final validation was performed by the Myla™ Team members belonging to the Product Validation functional area. Validation is done at the system level by integrating different systems including VITEK® MS. The software development cycle follows the standard IEC 62304.

Software Requirements Specification (SRS):

This specification summarizes the functional specifications for the VITEK®MS device software. This document defines requirements for the externally observable functions of the VITEK®MS Software. Three software product requirements were merged into a single summarized document and include the:

- Sample Preparation Station
- MS-ID Instrument Control software
- MS-ID Analysis Software

Traceability Analysis:

The Traceability Analysis Matrix lists the software requirements identified in the VITEK®MS and Myla™ Software Specification documents and relates these to the hazards that have been identified and to verification and validation testing.

The Traceability Analysis Matrix for the VITEK®MS Software and Myla™ Middleware are included in Sections 4.1.10, 4.2.7. The traceability matrix includes traceability from the PRD requirements to verification and validation test cases. It also includes traceability from the PRD to SRS. The SRS requirements were inherited from a third party software supplier and did not change during development.

Verification and Validation Testing:

This final validation report summarizes the results of the validation done on the mass spectrometry system (VITEK® MS V1.0, V1.1, V2, Myla™ V2, V2.2, V3.0, and V3.1). It includes the rationale, a brief description of the protocol, and a summary of the results including any deviations and justifications for any unresolved anomalies generated during validation.

The verification and validation test reports are acceptable as presented in the Sections listed above.

Revision Level History:

Software Item	Reviewed Revision
Acquisition Station Software	1.4.2
Prep Station Software	2.3.1
Knowledge Base	VITEK® MS KB v2.0
Computation Engine	1.1.0
Myla™	2.4

Unresolved Anomalies:

During the iterative verification testing of Myla™, there was a reduction of anomalies (582 total anomalies were repaired) and an increasing percentage of the testing passed verification. Following the 12th and final round of testing, 100 % of the unit and performance testing passed verification while 86% of the integration testing passed. The 14% of failures led to 42 unresolved anomalies. These anomalies were evaluated during an anomaly review board (ARB). Of the 42 resulting anomalies from verification testing, none were a level 1 or 2 (serious blocking anomalies), 10 were level 3 that had clear workarounds for the customer, and the remaining anomalies were either a minor inconvenience or transparent to the user. Only 4 of these 42 anomalies affected the VITEK®MS system directly and 2 of the 42 anomalies have been repaired in Myla™ V3.1. As the majority of these anomalies were considered minor and workarounds were in place for others, Myla™ 3.0 was considered verified and ready for validation

The system verification performed on the VITEK®MS components included: the analysis server software, prep station software, analysis server and computation engine, acquisition software, target slides, matrix, biological samples, Myla™, the LIS connection, and VITEK 2 connection. The system verification showed the testing done on the VITEK®MS system from versions 1.1 to 2.0 which is a complete testing of all the components in the VITEK®MS V2.0 system. Most of the system verification testing was done in V1.1. System verification was done on changes between V1.1 and V2.0. The verification strategies for the VITEK®MS V1.1 and 2.0 were organized in increments, by integrating more and more sub-components of the global system. In addition, several verification rounds were done to repair anomalies found during previous rounds. As mentioned above, the anomaly DCR 15190 found in the acquisition station was not verified at the system level but the software was verified and validated. This anomaly does not affect results. The system was considered verified at the system level.

For the VITEK®MS Software DCR's which were not fixed, a justification of why each DCR was not addressed and a severity was reported.

Any future issue or anomaly coming from the field will be analyzed with the help of the software manager, in collaboration with system engineers and Firm customer representatives through an Anomaly Review Board. The level the severity of the defect will drive the investigation activities and root cause analysis. Issues will be tracked and if a change is deemed necessary an impact analysis will be done to assess to potential effect on the software design, system, risks and Verification & Validation (V&V). Regression testing will be done in accordance to the potential impacts. Any release of a change shall be accepted by the Firm's QA/Regulatory Compliance teams.

Off the Shelf Software (OTS) or Software of Unknown Pedigree:

There were a total of 22 OTS applications reported in response to the Additional Information request. The manufacturer, released revision, and general and technical justification for use was included in the OTS report. The user does not directly interact with any OTS application and therefore no additional training is needed. The Firm has reported what testing was done during V&V activities and either indicates individual test cases as validation evidence or states how the OTS was validated as part of the system validation. A matrix is provided linking together which OTS is used by each VITEK®MS software component.

The implementation of the VILINK component is reported to use 3 OTS applications which are sufficiently documented. The VILINK provides remote access to the medical device via a periodic HTTPS connection. The security of this connection is described and documentation related to the use and cybersecurity features of VILINK are provided.

The 32 requirements of the CLSI AUTO-11AE standard were assessed. The software architecture has been designed to minimize IT security risks and the remaining level of risk is minor.

An OTS specific Risk Analysis is provided showing that all remaining risks are categorized as minor.

EMC Testing:

The system has been tested for compliance with the following standards:

Conformance to BS EN 61326-1, BS EN 61326-2-6:2006: Electrical equipment for measurement, control and laboratory use was reported. Additional conformance reported for testing of disturbance requirements including EM Field Immunity, Surge Immunity, Power magnetic field, Voltage dips and short interruptions according to the appropriate sections of IEC 610000-4.

Conformance to IEC 61010-1:2001 Safety requirements for electrical equipment for measurement, control and laboratory use Part 1was reported.

3. Specimen Identification:

The microorganisms to be identified must first be isolated on a suitable culture medium. Appropriate media, including commercial media most frequently used in clinical microbiology laboratories such as Columbia blood agar, should be used. The VITEK ®MS Prep Station software can be used to prepare samples for VITEK®MS and other systems, therefore several workflows are available to cover all possible analysis situations

The VITEK®MS Prep Station consists of a computer equipped with a barcode reader, and the VITEK MS®Prep Station Hardware. The VITEK MS Prep Station is used to prepare VITEK MS-DS target slides and to enter VITEK MS-DS data. These data are transferred from the VITEK® MS Prep Station to the VITEK®MS and Myla™ systems. The VITEK®MS Prep Station Hardware is connected via USB to the Prep Station.

VITEK®MS Sample Preparation screen

The VITEK®MS workflow begins with preparing the VITEK MS-DS target slides using the VITEK® MS Prep Station. Place a VITEK MS-DS target slide on the bench in front of the VITEK® MS Prep Station. The Sample Preparation screen on the VITEK®MS Prep Station is used to enter data linking specimens to VITEK MS-DS target slides and optionally to the VITEK 2 test cards. Data can be entered by scanning bar codes on the target slides and cards or by manually typing information in the appropriate fields. Once a bar code is scanned, the cursor will automatically move to the next required field.

VITEK®MS Target Slide Graphic

Once a target slide ID has been entered in the Enter Slide ID field, the system dynamically displays the status of a VITEK MS-DS target slide. Each time a Sample ID is linked with a VITEK®MS spot, the system updates the VITEK®MS target slide graphic and displays them as colored target slide spots (light blue for Fungi and dark blue for Bacteria). To display specimen information for a specific VITEK®MS target slide spot, the user clicks on a blue target slide spot. The user can then validate the entered sample information by clicking on the Validate button on the Prep Station screen or cancel all entered sample information by clicking on the Cancel button.

To further verify if the data entered for every spot are correct, the user can click on a filled target slide position. The software will then display the accession ID for the selected spot. In case of an error, all data entered for the selected spot can be erased. Once the VITEK MS-DS target slide is full or when sample preparation is finished, the user transfers the target slide information to the VITEK®MS system by clicking on the “Send Slide” button on the target slide graphic

4. Specimen Sampling and Handling:

All specimens, microbial cultures and inoculated products should be considered infectious and handled appropriately. Aseptic technique and usual precautions for handling organisms should be observed throughout this procedure. Refer to "CLSI M29-A, *Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline* - Current revision". For additional handling precautions, refer to "Biosafety in Microbiological and Biomedical Laboratories - CDC/NIH -Latest edition".

Isolated bacterial colonies are applied to a single well of a disposable, barcode-labeled target slide (Vitek MS-DS; bioMérieux, Inc.) using a 1.0 ul loop. The sample is applied as a thin layer to the target slide spot. For bacteria, the sample is overlaid with 1.0 ul of a saturated solution of alpha-cyano-4-hydroxycinnamic acid matrix in 50% acetonitrile and 2.5% trifluoroacetic acid (Vitek MS-CHCA; bioMérieux, Inc.), and air dried. For yeasts, a 1 µl loop is also used to apply the yeast sample to the target slide spot. 0.5 ul of MS-FA is added to the yeast and allowed to evaporate. 1.0 ul of MS-CHCA is then added to the same spot and air dried. A new pipet tip is used for each spot.

Prepared VITEK MS-DS slides must be tested within 48 hours. Prepared slides should be stored at room temperature until they are tested.

5. Calibration

E. coli ATCC 8739 is used to as a calibrator. This organism is deposited with VITEK MS-CHCA matrix on positions: xA1, xB1, xC1, of the MS-DS slides dependent on the number of samples tested (one calibrator per acquisition group of 16 spots). The VITEK®MS goes to the calibration spot in an acquisition group and performs a calibration. If the calibration passes, the instrument goes to the first spot in the acquisition group. If the calibration fails, an error is reported and VITEK®MS proceeds to the next acquisition group without collecting sample spectra. After spectra have been acquired from each sample spot in an acquisition group, the calibration spot is checked again. The calibration sample should provide E. *coli* identification at 99.9% in Myla™ software.

6. Quality Control

Two organisms are used for positive quality control. Matrix alone is used for the negative control. The quality control strains are as follows:

	Expected Result
Enterobacter aerogenes ATCC® 13048	*Enterobacter aerogenes*
Candida glabrata ATCC MYA-2950	*Candida glabrata*
Negative Control (matrix)	No Identification

NOTE: If the negative control gives does not give the expected result, users need to visually check the surface of the VITEK MS-DS target slides to ensure the slides are clean and repeat testing with new slide.

O. Other Supportive Instrument Performance Characteristics Data Not Covered In the "Performance Characteristics" Section above:

1. Mixed Culture Study

A strain of Staphyloccocus aureus direct from a colony, at minimum and maximum detection concentrations, mixed with other organisms with different ratios. Maximum concentrationwere standardized at 7 McFarland. Plate counts were performed to verify densities. Minimum concentrations suspension thresholds were evaluated at LoD of test organism. The following species were tested in this study: *Staphyloccocus aureus, Pseudomonas aeruginosa, Escherichia coli, Corynebacterium jeikeium* and *Candida glabrata*. VITEK®MS allowed an answer in:

- 68.2% (30/44) of cases, an identification of the more concentrated species in single choice.
- 11.4% (5/44) of cases, an identification of the less concentrated species in single choice (cases observed with *C. jeikeium*, which could be due to the fact that the limit of detection for *C. jeikeium* (6 McF) is close to the maximum tested concentration (7 McF), and
- 20.5% (9/44) of cases, a Low Discrimination between both tested species.

The user should follow manufacturer instructions to test pure isolated colonies only.

2. Viability Study:

A viability study to verify that there is no biological risk for the user to handle the spotted VITEK MS-DS slide once the VITEK MS-CHCA (bacteria) or VITEK MS-FA /VITEK MS-CHCA (yeast) is added was performed. A panel of strains comprising Gram negative, Gram positive and yeast groups were inoculated onto different media according to their growth requirements and incubated in appropriate conditions. Each organism was tested on the VITEK®MS using 24 hour and 3 day colony growth. The viability study showed that bacteria and yeast from a fresh culture spotted on the VITEK MS-DS target slides are not viable after the addition of CHCA matrix (bacteria) or CHCA matrix and formic acid (yeast).

NOTE: Although sporulation medium has not been validated for use with the VITEK®MS, studies demonstrated *Bacillus subtilis* from the sporulation medium (incubated for at least 4 days) is viable even after the addition of CHCA matrix. The viability of *Bacillus subtilis* from the sporulation medium appeared to be due to the presence of spores, after several days of incubation, which are able to survive in unfavorable conditions.

Users are instructed that all specimens, microbial cultures and inoculated products should be considered infectious and handled appropriately. Aseptic technique and usual precautions for handling organisms should be observed throughout this procedure. Refer to "CLSI M29-A, *Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline* - Current revision". For additional handling precautions, refer to "Biosafety in Microbiological and Biomedical Laboratories - CDC/NIH -Latest edition".

3. Run Failures from Clinical Trial:

Calibration failures (10 events), QC failures (4 events) and instrument failures (10 events) were documented and resolved during the clinical trial. Most calibration and QC failures were due to suboptimal sample preparation.

P. Proposed Labeling:

The labeling is sufficient and satisfies the requirements of 21 CFR Part 809.10, 21 CFR 801.109, and the special controls.

Q. Potential Risks and Required Mitigation Measures

Identified Potential Risk	Required Mitigation Measures
Incorrect identification of a pathogenic microorganism can lead to improper patient management.	1) Premarket notification submissions must include detailed documentation for device software, including, but not limited to, standalone software applications and hardware-based devices that incorporate software. 2) Premarket notification submissions must include database implementation methodology, construction parameters and quality assurance protocols.
Failure to correctly interpret test results	1) A detailed explanation of the interpretation of results and acceptance criteria must be included in the device's 21 CFR 809.10(b)(9) compliant labeling.
Failure to correctly operate the instrument	1) As part of the risk management activities performed as part of your 21 CFR 820.30 design controls, you must document an appropriate end user device training program that will be offered as part of your efforts to mitigate the risk of failure to correctly operate the instrument. 2) Premarket notification submissions must include details on the appropriate end user device training program that will be offered while marketing the device.

R. Benefit/Risk Analysis

Summary	
Summary of the Benefit(s)	The primary benefit from this device is more rapid identification of microorganisms from cultured material. In the setting of a critically ill patient or a patient infected by an unusual/unexpected pathogen, more rapid identification of a possible pathogen may ensure appropriate antibiotic use earlier; similarly, identification of a possible microbial contaminant (or non-pathogenic microorganism) may lead to earlier withdrawal of unnecessary antibiotics.
Summary of the Risk(s)	The risks from this device include incorrect identification of a pathogenic microorganism by the device. As noted earlier, device performance testing suggests that the overall risk of an incorrect identification is low, and that an incorrect identification may not necessarily translate to patient harm. Mitigating factors, including the nature of specific misidentification, patient clinical status, and experience of the clinical microbiologist (the latter is particularly important); in addition, antibiotic susceptibility testing should mitigate the risk that a patient will be treated with an antibiotic that is inactive against the isolated pathogen. (It is also possible that antibiotic susceptibility testing will raise suspicion that incorrect microorganism identification has occurred.) Overall, risk of patient injury from use of the device is low and should not be greater than alternatives currently used by clinical microbiology laboratories. Although a 'no identification' result may delay microorganism identification, this result would likely default to additional testing of the same sample or testing by an alternative method, and likely not present added risks relative to current clinical microbiology practice. Special controls regarding devices of this type introduce additional mitigations against possible device misidentification errors by requiring that premarket submissions include detailed documentation of device software (including, but not limited to, standalone software applications and hardware-based devices that incorporate software), and database implementation methodology, construction parameters and quality assurance protocols.

Summary of Other Factors	Microorganism identification is a core clinical laboratory function and is a mainstay of medical practice. The VITEK® MS reflects further evolution in the ability of laboratories to more rapidly identify pathogenic organisms and represents technology that, combined with widespread introduction of molecular technologies, will further add to the fundamental changes in clinical microbiology laboratory practice that have occurred over the past 10 – 15 years. Microorganism identification has an important role beyond individual patient care: it is essential for hospital infection control, for identification of possible outbreaks, and for bioterrorism alerts. To the extent that the VITEK®MS provides more rapid microorganism identification and the benefits that accrue, this is a potential advance over existing microbiological methods but not a complete replacement given the frequency of no identification results; this is well captured by the title of recent published study of VITEK®MS performance: Comparison of Vitek®MS (MALDI-TOF) to standard routine identification methods: an advance but no panacea. (Harris, P et al; Pathology 44(6), 583-585 (October, 2012). As noted earlier, device errors can arise from failure to operate the instrument correctly, or more broadly, failure to correctly interpret test results. These are mitigated by an appropriate end user device training program that will be to mitigate the risk of failure to correctly operate the instrument and by the device's 21 CFR 809.10(b)(9) compliant labeling where there is a detailed explanation of the interpretation of results and acceptance criteria.
Conclusions Do the probable benefits outweigh the probable risks?	Yes.

S. Conclusion:

The information provided in this *de novo* submission is sufficient to classify this device into class II under regulation 21 CFR 866.3361 with special controls. FDA believes that special controls, along with the applicable general controls, provide reasonable assurance of the safety and effectiveness of the device type. The device is classified under the following:

Device type: Mass spectrometer system for clinical use for the identification of microorganisms

Class: II (special controls)

Regulation: 21 CFR 866.3361

(a) *Identification*. A mass spectrometer system for clinical use for the identification of microorganisms is a qualitative *in vitro* diagnostic device intended for the identification of microorganisms cultured from human specimens. The device is comprised of an ionization source, a mass analyzer and a spectral database. The device is indicated for use in conjunction with other clinical and laboratory findings to aid in the diagnosis of bacterial and fungal infections.

(b) *Classification*. Class II (special controls). Mass spectrometer system for clinical use for the identification of microorganisms must comply with the following special controls:

1) Premarket notification submissions must include detailed documentation for device software, including, but not limited to, standalone software applications and hardware-based devices that incorporate software.

2) Premarket notification submissions must include database implementation methodology, construction parameters and quality assurance protocols.

3) A detailed explanation of the interpretation of results and acceptance criteria must be included in the device's 21 CFR 809.10(b)(9) compliant labeling.

4) As part of the risk management activities performed as part of your 21 CFR 820.30 design controls, you must document an appropriate end user device training program that will be offered as part of your efforts to mitigate the risk of failure to correctly operate the instrument.

5) Premarket notification submissions must include details on the appropriate end user device training program that will be offered while marketing the device.