EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR

DECISION MEMORANDUM

A. DEN Number:

DEN 170081

B. Purpose for Submission:

De Novo request for evaluation of automatic class III designation for the MALDI Biotyper CA System

C. Measurands:

See Indications for Use

D. Type of Test:

A mass spectrometer system for clinical use for the identification and differentiation of microorganisms is a qualitative *in vitro* diagnostic device intended for the identification and differentiation of microorganisms cultured from human specimens. The device is comprised of an ionization source, a mass analyzer and a spectral database. The system acquires, processes and analyzes spectra to generate data specific to a microorganism(s). 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:

Bruker Daltonik GmbH

F. Proprietary and Established Names:

Trade Name: MALDI Biotyper CA System

Common Names: MALDI Biotyper CA (MBT-CA) System, MBT-CA

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.3378

2. Classification:

Class II (Special Controls)

3. Product code(s):

QBN

4. Panel:

83- Microbiology

H. Indications for Use:

1. Indications for use:
The MALDI Biotyper CA System is a mass spectrometer system using matrix-assisted laser desorption/ionization - time of flight (MALDI-TOF) for the identification and differentiation of microorganisms cultured from human specimens.

The MALDI Biotyper CA System 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 fungal infections.

Bacteria:	
Abiotrophia defectiva	*Achromobacter xylosoxidans*
Acinetobacter baumannii / nosocomialis group	*Acinetobacter calcoaceticus*
Acinetobacter haemolyticus	*Acinetobacter johnsonii*
Acinetobacter junii	*Acinetobacter lwoffii*
Acinetobacter pittii	*Acinetobacter radioresistens*
Acinetobacter ursingii	*Actinomyces europaeus*
Actinomyces funkei	*Actinomyces graevenitzii*
Actinomyces hyovaginalis	*Actinomyces meyeri*
Actinomyces neuii	*Actinomyces odontolyticus*
Actinomyces oris	*Actinomyces radingae*
Actinomyces turicensis	*Actinomyces urogenitalis*
Actinotignum schaalii group	*Aerococcus sanguinicola*
Aerococcus urinae	*Aerococcus viridans*
Aeromonas salmonicida	*Aeromonas hydrophila / caviae* group
Aggregatibacter actinomycetemcomitans	*Aggregatibacter aphrophilus*
Aggregatibacter segnis	*Alcaligenes faecalis*
Alloiococcus otitis	*Alloscardovia omnicolens*

Bacteria:	
Anaerococcus murdochii	*Anaerococcus vaginalis*
Arthrobacter cumminsii	*Bacteroides caccae*
Bacteroides fragilis	*Bacteroides nordii*
Bacteroides ovatus group	*Bacteroides pyogenes*
Bacteroides salyersiae	*Bacteroides stercoris* group
Bacteroides thetaiotaomicron group	*Bacteroides uniformis*
Bacteroides vulgatus group	*Bifidobacterium breve*
Bordetella pertussis / bronchiseptica / parapertussis	*Bordetella hinzii*
Brevibacterium casei	*Brevundimonas diminuta* group
Burkholderia cepacia complex	*Burkholderia gladioli*
Burkholderia multivorans	*Campylobacter coli*
Campylobacter jejuni	*Campylobacter ureolyticus*
Capnocytophaga ochracea	*Capnocytophaga sputigena*
Chryseobacterium gleum	*Chryseobacterium indologenes*
Citrobacter amalonaticus complex	*Citrobacter freundii* complex
Citrobacter koseri	*Clostridium beijerinckii*
Clostridium bifermentans	*Clostridium butyricum*
Clostridium clostridioforme group	*Clostridium difficile*
Clostridium innocuum	*Clostridium paraputrificum*
Clostridium perfringens	*Clostridium ramosum*
Clostridium septicum	*Clostridium sordellii*
Clostridium sporogenes / Clostridium botulinum (group I)	*Clostridium tertium*
Corynebacterium accolens	*Corynebacterium afermentans* group
Corynebacterium amycolatum	*Corynebacterium aurimucosum* group
Corynebacterium bovis	*Corynebacterium coyleae*
Corynebacterium diphtheriae	*Corynebacterium freneyi*
Corynebacterium glucuronolyticum	*Corynebacterium glutamicum*
Corynebacterium jeikeium	*Corynebacterium kroppenstedtii*
Corynebacterium macginleyi	*Corynebacterium minutissimum*
Corynebacterium mucifaciens / ureicelerivorans group	*Corynebacterium propinquum*
Corynebacterium pseudodiphtheriticum	*Corynebacterium pseudotuberculosis*

Bacteria:	
Corynebacterium resistens	*Corynebacterium riegelii*
Corynebacterium striatum group	*Corynebacterium tuberculostearicum*
Corynebacterium ulcerans	*Corynebacterium urealyticum*
Corynebacterium xerosis	*Cronobacter sakazakii* group
Cupriavidus pauculus group	*Delftia acidovorans* group
Dermabacter hominis	*Dermacoccus nishinomiyaensis*
Edwardsiella tarda	*Eikenella corrodens*
Elizabethkingia meningoseptica group	*Enterobacter aerogenes*
Enterobacter amnigenus	*Enterobacter cloacae* complex
Enterococcus avium	*Enterococcus casseliflavus*
Enterococcus durans	*Enterococcus faecalis*
Enterococcus faecium	*Enterococcus gallinarum*
Enterococcus hirae	*Enterococcus mundtii*
Enterococcus raffinosus	*Escherichia coli*
Escherichia hermannii	*Escherichia vulneris*
Ewingella americana	*Facklamia hominis*
Finegoldia magna	*Fluoribacter bozemanae*
Fusobacterium canifelinum	*Fusobacterium necrophorum*
Fusobacterium nucleatum	*Gardnerella vaginalis*
Gemella haemolysans	*Gemella morbillorum*
Gemella sanguinis	*Granulicatella adiacens*
Haemophilus haemolyticus	*Haemophilus influenzae*
Haemophilus parahaemolyticus group	*Haemophilus parainfluenzae*
Hafnia alvei	*Helcococcus kunzii*
Kingella denitrificans	*Kingella kingae*
Klebsiella oxytoca / Raoultella ornithinolytica	*Klebsiella pneumoniae*
Klebsiella variicola	*Kocuria kristinae*
Kytococcus sedentarius	*Lactobacillus gasseri*
Lactobacillus jensenii	*Lactobacillus rhamnosus*
Lactococcus garvieae	*Lactococcus lactis*
Leclercia adecarboxylata	*Legionella longbeachae*

Bacteria:	
Legionella pneumophila	*Leuconostoc citreum*
Leuconostoc mesenteroides	*Leuconostoc pseudomesenteroides*
Listeria monocytogenes	*Macrococcus caseolyticus*
Mannheimia haemolytica group	*Micrococcus luteus*
Micrococcus lylae	*Mobiluncus curtisii*
*Moraxella sg Branhamella catarrhalis**	*Moraxella sg Moraxella nonliquefaciens**
*Moraxella sg Moraxella osloensis**	*Morganella morganii*
Myroides odoratimimus	*Myroides odoratus*
Neisseria bacilliformis	*Neisseria cinerea*
Neisseria elongata	*Neisseria flavescens / subflava* group
Neisseria gonorrhoeae	*Neisseria lactamica*
Neisseria meningitidis	*Neisseria sicca* group
Neisseria weaveri	*Nocardia brasiliensis*
Nocardia cyriacigeorgica	*Nocardia farcinica* group
Nocardia nova	*Nocardia otitidiscaviarum*
Ochrobactrum anthropi	*Oligella ureolytica*
Oligella urethralis	*Pantoea agglomerans*
Parabacteroides distasonis	*Parabacteroides goldsteinii*
Parabacteroides johnsonii / merdae group	*Parvimonas micra*
Pasteurella multocida	*Pediococcus acidilactici*
Pediococcus pentosaceus	*Peptoniphilus harei* group
Peptostreptococcus anaerobius	*Plesiomonas shigelloides*
Pluralibacter gergoviae	*Porphyromonas gingivalis*
Porphyromonas somerae	*Prevotella bivia*
Prevotella buccae	*Prevotella denticola*
Prevotella intermedia	*Prevotella melaninogenica*
Propionibacterium acnes	*Proteus mirabilis*
Proteus vulgaris group	*Providencia rettgeri*
Providencia stuartii	*Pseudomonas aeruginosa*
Pseudomonas fluorescens group	*Pseudomonas oryzihabitans*
Pseudomonas putida group	*Pseudomonas stutzeri*
Ralstonia pickettii	*Rhizobium radiobacter*

Bacteria:	
Rothia aeria	*Rothia dentocariosa*
Rothia mucilaginosa	*Salmonella* sp**
Serratia fonticola	*Serratia liquefaciens*
Serratia marcescens	*Serratia odorifera*
Serratia plymuthica	*Serratia rubidaea*
Sphingobacterium multivorum	*Sphingobacterium spiritivorum*
Sphingomonas paucimobilis group	*Staphylococcus aureus*
Staphylococcus auricularis	*Staphylococcus capitis*
Staphylococcus caprae	*Staphylococcus carnosus*
Staphylococcus cohnii	*Staphylococcus delphini*
Staphylococcus epidermidis	*Staphylococcus equorum*
Staphylococcus felis	*Staphylococcus haemolyticus*
Staphylococcus hominis	*Staphylococcus intermedius*
Staphylococcus lentus	*Staphylococcus lugdunensis*
Staphylococcus pasteuri	*Staphylococcus pettenkoferi*
Staphylococcus pseudintermedius	*Staphylococcus saccharolyticus*
Staphylococcus saprophyticus	*Staphylococcus schleiferi*
Staphylococcus sciuri	*Staphylococcus simulans*
Staphylococcus vitulinus	*Staphylococcus warneri*
Staphylococcus xylosus	*Stenotrophomonas maltophilia*
Streptococcus agalactiae	*Streptococcus anginosus*
Streptococcus canis	*Streptococcus constellatus*
Streptococcus dysgalactiae	*Streptococcus equi*
Streptococcus gallolyticus	*Streptococcus gordonii*
Streptococcus intermedius	*Streptococcus lutetiensis*
Streptococcus mitis / oralis group	*Streptococcus mutans*
Streptococcus parasanguinis	*Streptococcus pneumoniae*
Streptococcus pyogenes	*Streptococcus salivarius / vestibularis* group
Streptococcus sanguinis	*Streptococcus sobrinus*
Streptococcus thermophilus	*Sutterella wadsworthensis*
Trueperella bernardiae	*Turicella otitidis*
Vagococcus fluvialis	*Veillonella parvula* group

Bacteria:	
Vibrio parahaemolyticus	Vibrio vulnificus
Weeksella virosa	Yersinia enterocolitica
Yersinia frederiksenii	Yersinia intermedia
Yersinia kristensenii	Yersinia pseudotuberculosis
* = subgenus	
sp** = species	

Yeasts:	
Candida albicans	Candida auris
Candida boidinii	Candida dubliniensis
Candida duobushaemulonii	Candida famata
Candida glabrata	Candida guilliermondii
Candida haemulonis	Candida inconspicua
Candida intermedia	Candida kefyr
Candida krusei	Candida lambica
Candida lipolytica	Candida lusitaniae
Candida metapsilosis	Candida norvegensis
Candida orthopsilosis	Candida parapsilosis
Candida pararugosa	Candida pelliculosa
Candida tropicalis	Candida valida
Candida zeylanoides	Cryptococcus gattii
Cryptococcus neoformans var grubii*	Cryptococcus neoformans var neoformans*
Cyberlindnera jadinii	Geotrichum candidum
Geotrichum capitatum	Kloeckera apiculata
Malassezia furfur	Malassezia pachydermatis
Pichia ohmeri	Rhodotorula mucilaginosa
Saccharomyces cerevisiae	Trichosporon asahii
Trichosporon inkin	Trichosporon mucoides group
* = variety	

2. Special conditions for use statement(s):

For in vitro diagnostic use only

The MALDI Biotyper CA System is for prescription use only.

Special instrument requirements:

Microflex LT/SH mass spectrometer

Database: MALDI Biotyper for Clinical Applications (MBT-CA)

Software:
- MBT-CA System Software Package:
- MBT-CA System client software displaying the user interface
- MBT-CA System Server
- MBT-CA System DB Server
- flexControl Software Package (GTPS firmware, flexControl acquisition software)

Honeywell (Hyperion 1300g) Barcode Reader (optional)

I. Device Description:

- The MBT-CA System consists of the Microflex LT/SH mass spectrometer, reference library, kit reagents (US IVD HCCA, US IVD Bacterial Test Standard), US IVD 48 Spot Target or MBT Biotarget 96 US IVD plate, and software. The MALDI Biotyper CA System with closed safety covers is a Class 1 Laser product. With the safety cover opened it becomes a Class 4 Laser product.
- The MALDI Biotyper CA System reference library was established by analyzing the type strain from each claimed species combined with 4 to ~30 additional strains from the same species provided by clinical laboratories or commercial strain collections. Currently a total of 3029 strains (covering 334 species / groups with 294 bacteria plus 40 yeasts) are contained in the clinically validated MBT-CA library.
- Implementation methodology, construction parameters and quality assurance protocols use a standard operating protocol for generation of reference entries and all testing parameters are the same.
- MBT-CA microorganism identification is based on isolate MALDI spectra using Bruker reference libraries with a 1:1 comparison of unknown MALDI spectra against each single entry of a given reference library. During a single identification event, an unknown MALDI spectra is compared against each single reference entry producing (b) (4) individual log(score) results. This number of log(scores) is sorted based on their value and the highest one is used to generate the final result. The addition of new reference entries does not influence the already included entries. If no reference entries are removed within a library update the log(score) calculation remains unchanged for the same MALDI spectra.
- MALDI Biotyper CA System client software displays a user-interface which guides the user through the MALDI Biotyper CA System workflow. The MALDI Biotyper CA System client also interfaces to the flexControl software for automated acquisition of mass spectra on the microflex LT/SH instrument.
- The MALDI Biotyper CA System server communicates with the MALDI Biotyper CA System client and the MBT-DB server. It performs preprocessing on acquired spectra, and

matches peak lists against the Main Spectrum (reference pattern, (MSP)) for matching and calculates the score value (log (score)).

- The MBT-DB server stores all information for the MALDI Biotyper CA System. The MBT-DB maintains spectra data (creation information and mass/intensity lists), project data (results of defined and executed runs), method data (parameter lists for spectra preprocessing and identification), user management data, reference patterns and other peak lists plus additional maintenance data.
- GTPS firmware communicates with the flexControl PC software, controls and monitors the vacuum, moves the sample carrier and performs the docking of the target plate, controls and monitors high voltages in the ion source, generates trigger signals, and monitors instrument status.
- The flexControl acquisition software communicates with the MALDI Biotyper CA System client, loads automatic run jobs, communicates with the GTPS firmware, communicates with the laser in the microflex LT/SH instrument, sets the acquisition parameters in the digitizer and reads the acquired data from the digitizer, performs automated data acquisition, evaluates acquired spectra, adjusts the laser power during automatic data acquisition, performs a re-calibration of the time-of-flight to mass transformation, stored acquired spectra on disk and performs source cleaning. The flexControl software does not display a user interface.
- The optional Honeywell (Hyperion 1300g) Barcode Reader USB cable is connected to the MALDI Biotyper CA System computer. The barcode reader scans the unique ten-digit target ID which appears in the Target ID box on the target plate. After the target ID has been entered, the a new Run page opens and the ten-digit target ID appears as the Plate ID and is appended to the Run name. Sample identifications are entered into the computer corresponding to the target plate position for that run.

Required Materials Supplied by Bruker
- US IVD 48 Spot Target [P/N: 8604532]
- US IVD BTS (Bacterial Test Standard) [P/N: 8604530]
- US IVD HCCA portioned [P/N: 8604531]

Required Materials that are Not Supplied by Bruker
The following solvents and chemicals are not supplied by Bruker but are required to perform the analysis. For best results, use freshly prepared solutions and chemicals of (b) (4) or MALDI compatible grade (for example, (b) (4) (b) (4) solvents).

- Standard Solvent (acetonitrile 50%, water 47.5% and trifluoroacetic acid 2.5%) [Vendor: (b) (4) or equivalent]
- Acetonitrile
- (b) (4) water
- Formic acid (FA)
- (b) (4) Ethanol (EtOH)
- Trifluoroacetic acid (TFA)
- Sterile Colony Transfer Device
- Sterile (b) inoculation loops
- (b) (4) pipette tips (b) (4)
- Suitable pipettes for volumes from (b) (4)

- ▊▊▊ (b) (4) plastic tubes, (b) mL [Vendor: (b) (4)]
- Screw-cap micro tubes ▊▊▊▊ (b) (4) and screw caps (b) (4)
- Bench-top microcentrifuge capable of ▊▊▊ (b) (4)
- Vortex mixer
- Standard laboratory equipment

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

Not applicable

K. Test Principle:

Organisms to be identified with the MALDI Biotyper CA System are isolated using the appropriate isolation media. Users are instructed to first test the organism using the direct transfer technique (unless specified to perform extraction in the product labeling). If results are less than <2.0 log(score), users are then directed to perform extraction (eDT or EXT) procedure.

- Direct Transfer (DT): An individual colony from an overnight subculture plate is transferred to a selected position on an US IVD 48 Spot Target (target). The target is air dried and US IVD HCCA portioned (matrix) is added. The standard solvent (50% acetonitrile / 47.5% H_2O / 2.5% trifluoroacetic acid) in the matrix solution extracts proteins (mainly ribosomal proteins, which are present in high concentration) from the microorganisms. When dried matrix crystallizes, the inoculated target is ready to be analyzed on the MALDI Biotyper CA System.
- extended Direct Transfer (eDT): An isolated colony of bacteria or yeast is transferred as a thin film directly onto a sample position on a cleaned target. The sample spot is overlayed with 1 µL 70% aqueous formic acid directly on the target plate and allowed to dry at room temperature. Afterwards the spots are overlayed with US IVD HCCA portioned (matrix) and allowed to dry. When dried matrix crystallizes, the inoculated target is ready to be analyzed on the MALDI Biotyper CA System.
- Extraction Procedure (Ext): For this purpose, isolated colonies from the overnight subculture plate are extracted using an ethanol/formic acid procedure. Afterwards they are transferred to the target plate and allowed to dry. Afterwards the spots are overlaid with US IVD HCCA portioned (matrix) and allowed to dry. When dried matrix crystallizes, the inoculated target is ready to be analyzed on the MALDI Biotyper CA System.
- Samples are analyzed using MALDI (matrix-assisted laser desorption/ionization)-TOF (time-of-flight) mass spectrometry. The matrix transfers protons onto the extracted proteins and absorbs UV light. After complete drying, the mixture is exposed to laser pulses, resulting in energy transfer from the matrix causing evaporation and release of positively charged intact proteins and peptides ("soft" ionization technique). The ionized molecules are accelerated by electrical potentials through a flight tube to the mass spectrometer, with separation of the particles determined by their mass/charge ratio (m/z). As different proteins/peptides have different masses, ions arrive at the detector at different times (time of flight). The system measures the time (in the nanosecond range) between pulsed acceleration and the corresponding detector signal, and the speed is then converted into an exact molecular mass. The mass-to-charge ratio of an ion is proportional to the square of its drift

time. Highly abundant microbial proteins (mainly ribosomal proteins) result in a mass spectrum with characteristic mass and intensity distribution. It is species-specific for many bacteria and is interpreted as a molecular fingerprint to identify the test organism. Data acquisition is controlled with MALDI Biotyper CA System Software. The spectrum of the unknown organism is first transformed into a peak list. This peak list is compared to the reference peak list of each organism found in the reference library (database) and a log(score) is generated. See Assay Cut-Off.

L. Performance Characteristics:

1. *Analytical performance:*

   a. <u>Addition of *C. auris* to MBT-CA reference library</u>

   A panel of *Candida auris* isolates and nine (9) other yeast species related to *C. auris* or commonly misidentified as *C. auris* were obtained from the CDC & FDA Antibiotic Resistance Isolate Bank (https://wwwn.cdc.gov/arisolatebank/). Additional *C. auris* isolates were obtained from (b) (4) (9), (b) (4) (8), (b) (4) (1). Isolates are summarized in Table 1 below.

   Twenty-eight (28) *C. auris* isolates as well as the nine (9) additional yeast species of the CDC panel were used for this study. Each isolate was cultured on sabouraud-dextrose agar, and spotted 8 times using DT, eDT and Ext sample preparation techniques. and measured on the MALDI instrument. Mass spectra acquisition and MBT-CA System identification were performed using FDA-cleared MBT-CA System software (client version 3.2.12). 888 spectra (37 strains * 3 sample preparations * 8 spots = 888) were used for identification and compared against the:
   - cleared validated MBT-CA library,
   - non-clinically validated MBT-CA library,
   - cleared plus non-clinically validated MBT-CA libraries, and
   - cleared validated MBT-CA library plus the six (6) new *C. auris* reference entries.

   All 37 isolates used in this study were identified successfully using DT, eDT and Ext sample preparation techniques. Six (6) strains were used for reference library generation and 28 strains of *C. auris* were analyzed. All 28 strains were used for performance evaluation but only 22 strains were used for generating the truth tables; the six (6) strains used for reference entries were excluded from truth table counting (See Tables 2 and 3).
   The ITS sequence was determined for all six strains used for the new reference library entries.

Table 1: All *Candida auris* and *Candida auris*-related strains used in this study

Strain ID		Resource Centre		Comment
Candida auris (b) (4)		(b) (4)		reference strain
Candida auris				reference strain
Candida auris				reference strain

Candida auris	(b) (4)	field strain
Candida auris		field strain
Candida auris		field strain
Candida auris		field strain
Candida auris		field strain
Candida auris		field strain
Candida auris		field strain
Candida auris		field strain
Candida auris		field strain
Candida auris		field strain
Candida auris		field strain
Candida auris		field strain
Candida auris		field strain
Candida auris		field strain
Candida auris		reference strain
Candida auris AR0381_CAU_01 CDC	CDC, USA	"*C. auris* panel"
Candida auris AR0382_CAU_02 CDC	CDC, USA	"*C. auris* panel"
Candida auris AR0383_CAU_03 CDC	CDC, USA	"*C. auris* panel"
Candida auris AR0384_CAU_04 CDC	CDC, USA	"*C. auris* panel"
Candida auris AR0385_CAU_05 CDC	CDC, USA	"*C. auris* panel"
Candida auris AR0386_CAU_06 CDC	CDC, USA	"*C. auris* panel"
Candida auris AR0387_CAU_07 CDC	CDC, USA	"*C. auris* panel"
Candida auris AR0388_CAU_08 CDC	CDC, USA	"*C. auris* panel"
Candida auris AR0389_CAU_09 CDC	CDC, USA	"*C. auris* panel"
Candida auris AR0390_CAU_10 CDC	CDC, USA	"*C. auris* panel"
Candida duobushaemulonii AR0391_CAU_11 CDC	CDC, USA	"*C. auris* panel"
Candida duobushaemulonii AR0392_CAU_12 CDC	CDC, USA	"*C. auris* panel"
Candida duobushaemulonii AR0394_CAU_14 CDC	CDC, USA	"*C. auris* panel"
Candida haemulonii AR0393_CAU_13 CDC	CDC, USA	"*C. auris* panel"
Candida krusei AR0397_CAU_17 CDC	CDC, USA	"*C. auris* panel"
Candida lusitaniae AR0398_CAU_18 CDC	CDC, USA	"*C. auris* panel"
Kodameae ohmeri AR0396_CAU_16 CDC	CDC, USA	"*C. auris* panel"
Saccharomyces cerevisiae AR0399_CAU_19 CDC	CDC, USA	"*C. auris* panel"

Table 2: *C. auris* Performance (MBT-CA results vs Reference Algorithm)

	Candida auris			
MBT-CA Result	Reference Algorithm			Total
	High resolution species	Low resolution species/genus	Negative	
Positive Organism ID; (High Confidence); log(score) ≥2.0	22	0	0	22
Positive Organism ID; (Low Confidence); log(score) ≥1.7 - <2.0	0	0	0	
Incorrect MBT-CA (≥1.7) No ID	0	0	n/a	
Total	22			22

b. *Analytical Specificity:*

Interference and specificity studies were previously reported in 510(k) K130831. For the addition of *C. auris* to the MBT-CA reference library, the following studies were conducted.

In silico evaluation:

To determine whether cross identifications would occur due to the MBT-CA library update (i.e., cleared MBT-CA library + *C. auris*), a subset of stored spectra for previously claimed organisms was run against the current as well as the updated reference library to verify that performance for these analytes was identical. In this study (b)(4) spectra were compared against the current validated and the updated validated MBT-CA library. The selected spectra covered all claimed species (b) (4) species), each sample preparation technique (b) (4) and a spectru expected results ("no ID", "low confidence ID" and "high confidence ID").

The cross-validation showed 100% identical results. Each single log(score) of the 6822 log(scores) was identical before and after the library update demonstrating that adding a new reference entry does not influence the identification results of prior library versions.

Wet testing of claimed organisms:

A predefined and well characterized set of (b)(4) leared species (see Table 3 below) was tested using the current MBT-CA libr s (validated plus non-clinically validated) as well as the modified MBT-CA libraries (deletion of three *C. auris* entries of the non-clinically validated library, inclusion of six new *C. auris* entries in the validated library). The established extraction and spotting procedures were used to verify that performance for this test set is similar for the modified and the previously cleared MBT-CA library. Each of the (b)(4) elected, claimed species were each measured in triplicates. All three sample pre tion techniques (DT, eDT and

Ext) were applied independent from the identification success of DT and/or eDT sample preparation. All sample spots were measured on two different instruments. Overall 360 spectra / log(scores) were analyzed. All organisms could be identified using the established spotting algorithm (i.e., DT, eDT, EXT). No influence of the new *C. auris* reference entries and no cross-identification was observed.

Table 3: "Wet Testing" - cleared organisms

Microorganisms			
Group		Species	Resource Centre Strain ID
Gram neg. bacteria	Aerobe	*Escherichia coli*	(b) (4)
		Klebsiella pneumoniae	
		Pseudomonas aeruginosa	
	Anaerobe	*Bacteroides fragilis*	
Gram pos. bacteria	Aerobe	*Enterococcus faecalis*	
		Staphylococcus aureus	
		Streptococcus pneumoniae	
	Anaerobe	*Clostridium perfringens*	
Yeasts		*Candida albicans*	
		Candida glabrata	

Wet testing of RUO organisms:

To verify that no cross-identifications between the Research Use Only (RUO) and the MBT-CA libraries occurs, three replicates of nine (9) species (see Table 4 below) which are in the RUO library (but are not in the claimed library or the non-clinically validated library) were tested against the MBT-CA old and updated libraries. All three sample preparation techniques (DT, eDT and Ext) were applied independent from the identification success of DT and/or eDT sample preparation. All organisms were tested on two instruments. The MBT-CA identification was performed using the current MBT-CA libraries (validated plus non-clinically validated) as well as the modified MBT-CA libraries (deletion of three (3) C. *auris* entries of the non-clinically validated library, inclusion of six (6) new C. *auris* entries in the validated library). Overall (b) pectra / log(scores) were analyzed. None of the RUO organisms were (4) ified with the MBT-CA libraries. No influence of the new *C. auris* reference entries and no cross-identification was observed.

Table 4:"Wet Testing" - RUO organisms

Microorganisms			
Group		Species	Resource Centre Strain ID
Gram neg. bacteria	Aerobe	*Acinetobacter gerneri*	(b) (4)
		Chryseobacterium chaponense	
		Flavobacterium flevense	
		Pantoea calida	

Gram pos. bacteria	Aerobe	*Micrococcus flavus*
		Rothia terrae
	Anaerobe	*Clostridium magnum*
		Paenibacillus durus
Yeasts		*Candida solani*

c. *Reproducibility:* See K130831, K142677 and K163536.

d. *Linearity/assay Reportable Range:* Not applicable, qualitative assay.

e. *Traceability, Stability, Expected Values (controls, calibrators, or methods):*

   Calibrator: See K130831, K142677 and K163536.

   Controls: See K130831, K142677 and K163536.

   Sample Stability after Matrix Overlay: The sample stability study on target plates for Gram-negative bacteria was previously validated and reported in 510(k) K130831. The sample stability on target plates for Gram-positive bacteria and yeasts was validated and reported in 510(k) K142677.

   US IVD Bacterial Test Standard (BTS) Stability: BTS Stability was established and described in 510(k) K130831.

   HCCA portioned (Matrix) Stability: CCA portioned (Matrix) Stability was established and described in 510(k) K130831.

   Target plates stability: Target plate stability was established and described in 510(k) K142677.

   Organism Stability: For FDA-cleared media organism stability studies see K130831, K142677 and K163536.

f. *Detection Limit:*

   The Limit of Detection/Dynamic Range study for Gram-negative bacteria was previously performed and reported in K130831. The Limit of Detection/Dynamic Range study for Gram-positive bacteria and yeasts was performed and reported in 510(k) K142677.

g. *Influence of Agar Media*

   The validation of sample preparation of test organism to demonstrate that culture media inoculated onto US IVD 48 spot targets with or without an organism present does not interfere with system performance was previously performed and reported in 510(k) K130831.

h. Carry-Over/ Cross-Contamination
The carry-over, cross-contamination and target cleaning study was previously performed and reported in K130831.

i. Assay Cut-off

The assay cut-off remains unchanged as established in K130831. Using statistical analysis, a probability ranking of the organism identification is generated. The probability ranking is represented as a log (score) between 0.00 and 3.00.

Organism identification (direct or extracted) is reported with high confidence if the log(score) is ≥ 2.00. If a direct transfer organism identification log(score) is <2.00; the user is instructed to follow an extraction procedure (eDT or EXT).

After extraction:
- If the organism identification log(score) is between 1.7 and <2.0, the identification is reported as low confidence.
- If the organism identification log(score) is <1.7, it is reported as 'No Identification'.

Some MBT-CA identifications results are non-clinically validated organisms and are displayed in the MBT-CA report in the interest of public health as a means of directing the required additional laboratory testing. Non-clinically validated organism results are created from reference patterns which have not been clinically validated. 'No Identification' is reported based on the validated reference pattern (MSP) library if a result from the non-clinically validated reference pattern (MSP) library was found to yield a higher log(score) value. The non-clinically validated result is added as a comment (grey in square brackets) below the 'No Identification' result. 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 MBT-CA to the laboratory information system.

The log(score) value ranges defined in the MBT-CA reflect the probability of organism identification. Results should be reviewed by a trained microbiologist and final organism identification should be based on all relevant information available. This information includes, but is not limited to, Gram staining, colony morphology, growth characteristics, sample matrix, or other factors that might impact organism identification.

If an indication for the possibility of cross-matching patterns (i.e., cross-identification) was found during the clinical or analytical performance studies (see K130831, K142677 and K163536), a matching hint was placed for the organism in the package labelling (matching hint table).

2. Comparison Studies:

a. Method comparison with predicate device: Not applicable.

    b. Matrix comparison: Not applicable.

3. <u>Clinical Studies</u>: See K130831, K142677 and K163536.

4. <u>Clinical cut-off</u>**:** See Assay Cut-Off.

5. <u>Expected values/Reference range:</u> See L.1.i.

M. Instrument Name(s)

Microflex LT/SH mass spectrometer

N. System Descriptions: See K130831, K142677 and K163536

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

See K130831, K142677 and K163536

P. Proposed Labeling:

The labeling is sufficient and satisfies the requirements of 21 CFR parts 801 and 809 as well as the Special Controls for this type of device.

Q. Identified Risks to Health and Mitigation Measures:

Identified Risks to Health and Mitigation Measures

Identified Risks to Health	Mitigation Measures
Incorrect identification or lack of identification of a pathogenic microorganism	Special Controls 1, 2, 3, 4
Failure to correctly interpret test results	Special Control (3)
Failure to correctly operate the instrument	Special Control (3)(i), (5)(iv)(H)

R.   Benefit/Risk Analysis:

Summary	
Summary of the Benefit(s)	The primary benefit from this device is more rapid and accurate identification of *Candida auris* from cultured material. In the setting of a critically ill patient, more rapid identification of pathogens, such as *C. auris*, may ensure appropriate antimicrobial use and patient isolation precautions earlier.
Summary of the Risk(s)	The primary risk associated with use of this device is incorrect identification of *C. auris* or other pathogenic microorganisms. If an organism misidentification, or 'no identification' was to occur, patients could potentially experience a delay in effective antimicrobial therapy, with associated increases in morbidity or mortality. However, since its introduction into the clinical microbiology laboratory, MALDI-TOF has been found to be highly accurate for claimed microorganisms, with few reports of misidentification resulting in patient harm. 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.
Summary of Other Factors	None.

Conclusions
Do the probable benefits outweigh the probable risks?

The probable benefits of the MBT-CA system outweigh the potential risks in light of the listed special controls and applicable general controls. An identification for *C. auris* and protocol for future database updates will provide patients access to rapid and accurate laboratory results. The validation data, in association with clinical experience using MALDI-TOF technology, suggest that errors will be uncommon and unlikely to result in patient harm. The risks of patient harm are further mitigated by the proposed special controls, including product labelling, and current laboratory practices, which include alternative identification methods, AST testing, and other diagnostics.

S. Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

T. Conclusion:
The information provided in this De Novo submission is sufficient to classify this device into class II under regulation 21 CFR 866.3378. FDA believes that the stated special controls, and applicable general controls, provide reasonable assurance of the safety and effectiveness of the device type. The device is classified under the following:

Product Code: QBN
Device Type: Clinical Mass Spectrometry Microorganism Identification and Differentiation System
Class: II (special controls)
Regulation: 21 CFR 866.3378

(a) Identification. A clinical mass spectrometry microorganism identification and differentiation system is a qualitative in vitro diagnostic device intended for the identification and differentiation of microorganisms from processed human specimens. The system acquires, processes, and analyzes spectra to generate data specific to a microorganism(s). The device is indicated for use in conjunction with other clinical and laboratory findings to aid in the diagnosis of bacterial and fungal infection.

(b) *Classification.* Class II (special controls). Clinical mass spectrometry microorganism identification and differentiation system must comply with the following special controls:

(1) The intended use for the 21 CFR 809.10 labeling must include a detailed description of what the device detects, the type of results provided to the user, the clinical indications appropriate for test use, and the specific population(s) for which the device is intended, when applicable.

(2) Any sample collection device used must be FDA-cleared, -approved, or -classified as 510(k) exempt with an indication for in vitro diagnostic use.

(3) The 21 CFR 809.10(b) labeling must include:

    (i)   A detailed device description, including all device components, control elements incorporated into the test procedure, instrument requirements, ancillary reagents required but not provided, and a detailed explanation of the methodology and all pre-analytical methods for processing of specimens, and algorithm used to generate a final result. This must include a description of validated inactivation procedure(s) that are confirmed through a viability testing protocol, as applicable.

    (ii)   Performance characteristics for all claimed sample types from analytical studies with clinical specimens that include prospective samples and/or, if appropriate, characterized samples.

    (iii)   Performance characteristics of the device for all claimed sample types based on analytical studies, including, but not limited to, limit of detection, inclusivity,

reproducibility, interference, cross reactivity, interfering substances, carryover/cross contamination, sample stability, and additional studies regarding processed specimen type and intended use claims, as applicable.

    (iv)   A detailed explanation of the interpretation of test results for clinical specimens and acceptance criteria for any quality control testing.

(4) The device's labeling must include a prominent hyperlink to the manufacturer's website where the manufacturer shall make available their most recent version of the device's 21 CFR 809.10(b) labeling, which must reflect any changes in the performance characteristics of the device. FDA must have unrestricted access to this website or manufacturers must provide this information to FDA through an alternative method that is considered and determined by FDA to be acceptable and appropriate.

(5) Design verification and validation must include:

    (i)   Any clinical studies must be performed with samples representative of the intended use population and compare the device performance to results obtained from an FDA accepted reference method and/or FDA accepted comparator method, as appropriate. Documentation from the clinical studies must include the clinical study protocol (including predefined statistical analysis plan, if applicable), clinical study report, and results of all statistical analyses.

    (ii)   Performance characteristics for analytical and clinical studies for specific identification processes for the following, as appropriate:

        (A) Bacteria
        (B) Yeasts
        (C) Molds
        (D) Mycobacteria
        (E) Nocardia
        (F) Direct sample testing (e.g., Blood culture)
        (G) Antibiotic resistance markers
        (H) Select Agents (e.g., pathogens of high consequence)

    (iii)   Documentation that the manufacturer's risk mitigation strategy ensures that their device does not prevent any device(s) with which it is indicated for use, including incorporated device(s), from achieving their intended use (e.g., safety and effectiveness of the functions of the indicated device(s) remain unaffected).

    (iv)   A detailed device description including the following:

        (A) Overall device design, including all device components and all control elements incorporated into the testing procedure.

        (B) Algorithm used to generate a final result from raw data (e.g., how raw signals are converted into a reported result).

(C) A detailed description of device software, including, but not limited to, validation activities and outcomes.

(D) Acquisition parameters (e.g., mass range, laser power, laser profile and number of laser shots per profile, raster scan, signal-to-noise threshold) used to generate data specific to a microorganism.

(E) Implementation methodology, construction parameters, and quality assurance protocols, including the standard operating protocol for generation of reference entries for the device.

(F) For each claimed microorganism characteristic, each organism must have a minimum of five reference entries (including the type strain for microorganism identification) or, if there are fewer reference entries, a clinical and/or technical justification, determined by FDA to be acceptable and appropriate, for why five reference entries are not needed.

(G) All type strains and at least 20 % of the non-type strains of a species detected by the device must be characterized by DNA sequence analysis or, if there are fewer strain sequences, then a clinical and/or technical justification, determined by FDA to be acceptable and appropriate, for the reduced number of strains sequenced must be provided.

(H) As part of the risk management activities, an appropriate end user device training program must be offered as an effort to mitigate the risk of failure from user error.

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