BD MAX™ MDR-TB

REF **443878**

For *In Vitro* Diagnostic Use
For use with the BD MAX™ System

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English

INTENDED USE

The BD MAX™ Multi Drug Resistant Tuberculosis (MDR-TB) assay, performed on the BD MAX System, is an automated qualitative *in vitro* diagnostic test for the direct detection of *Mycobacterium tuberculosis* complex (MTBC) DNA in raw sputum or concentrated sputum sediments prepared from induced or expectorated sputa. In specimens where MTBC DNA is detected, BD MAX MDR-TB also detects mutations in the *rpoB* gene associated with rifampin resistance as well as mutations in the *katG* gene and *inhA* promoter region both of which are associated with isoniazid resistance.

The test utilizes real-time polymerase chain reaction (PCR) for the amplification of specific DNA targets and fluorogenic, target-specific hybridization probes to detect MTBC DNA as well as the DNA associated with mutations in the *rpoB* and *katG* genes and the *inhA* promoter region associated with multidrug resistant TB.

The BD MAX MDR-TB assay is intended for use with specimens from patients for whom there is clinical suspicion of tuberculosis (TB) and who have not received anti-tuberculosis therapy, or less than three days of therapy in the past six months. This test is intended as an aid in the diagnosis of pulmonary tuberculosis when used in conjunction with clinical and other laboratory findings.

SUMMARY AND EXPLANATION OF THE PROCEDURE

Tuberculosis (TB) is an infectious disease caused by the *M. tuberculosis* complex (MTBC) species and remains a major global health problem causing an estimated 10.4 million cases and 1.7 million deaths annually.[1] Multidrug-resistant TB (MDR-TB) is a continued threat and a more complicated form of the disease due to MTBC resistant to both rifampin (RIF) and isoniazid (INH).[1] In 2016, there were 600,000 new cases with resistance to rifampin (RRTB), the most effective first-line drug, of which 490,000 had multidrug-resistant TB (MDR-TB).[1] In 2016, WHO released new TB testing guidelines calling for rapid molecular tests for MDR-TB detection.[2] Rapid and accurate detection of MTBC and drug resistance forms of it is important to appropriately identify and treat patients suffering with the disease to help reduce the death rate and stop the spread of TB.[3]

The BD MAX MDR-TB assay delivers an integrated result for MTBC (multicopy genomic targets IS6110 and IS1081 as well as a single copy genomic target), RIF (RRDR codons 507-533) and INH (*inhA* promoter region and *katG* 315 codon) resistance, and automates the testing process and minimizes operator intervention from the time the sample is placed onto the BD MAX System until results are available. The BD MAX MDR-TB assay performed on the BD MAX System, can provide results for 24 specimens in less than 4 hours, as compared to traditional culture methods and drug resistance tests which can take weeks.

PRINCIPLES OF THE PROCEDURE

Raw sputum or concentrated sputum sediments prepared from induced or expectorated sputa are collected from subjects and transported to the laboratory in leak-proof collection container. A dilution of the specimen is prepared in the collection container with BD MAX STR, so that the final ratio of STR:Specimen is 2:1. The collection container is then shaken 10 times, incubated at room temperature for 5 minutes and shaken vigorously again 10 times. The BD MAX STR-treated sample is then incubated at room temperature for 25 minutes. Using a BD MAX Transfer Pipet, 2.5 mL of the STR-treated sample is transferred to a labeled BD MAX MDR-TB Sample Tube. The BD MAX MDR-TB Sample Tube is closed with a septum cap and transferred to the BD MAX System. Once the work list is generated and the specimen is loaded on the BD MAX instrument, along with a BD MAX MDR-TB Unitized Reagent Strip and PCR Cartridge, the run is started and no further operator intervention is required. The BD MAX System automates specimen preparation, including target organism lysis, DNA extraction and concentration, reagent rehydration, target nucleic acid sequence amplification and detection using real-time PCR. The interpretation of the signal is performed automatically by the BD MAX System. The assay also includes a Sample Processing Control that is provided in the Extraction Tube and subjected to extraction, concentration and amplification steps. The Sample Processing Control monitors for the presence of potential inhibitory substances as well as system or reagent failures.

The BD MAX System uses a combination of reagents and heat to perform cell lysis and DNA extraction. Released nucleic acids are captured by magnetic affinity beads. The beads, with the bound nucleic acids, are washed and the nucleic acids are eluted by heat in the Elution Buffer. Eluted DNA is neutralized and transferred to the Master Mix tubes to rehydrate the PCR reagents. After rehydration, the BD MAX System dispenses a fixed volume of PCR-ready solution into the BD MAX PCR Cartridge. Microvalves in the BD MAX PCR Cartridge are sealed by the system prior to initiating PCR to contain the amplification mixture thus preventing evaporation and amplicon contamination.

The amplified DNA targets are detected using hydrolysis (TaqMan®) probes labeled at one end with a fluorescent reporter dye (fluorophore) and at the other end with a quencher moiety. Probes labeled with different fluorophores are used to detect *M. tuberculosis* complex DNA, rifampin resistance, isoniazid resistance and Sample Processing Control amplicons in the five different optical channels of the BD MAX System. Rifampin resistance detection utilizes melt chemistry by detecting mutations in the 81 base pair region of RRDR of the *rpoB* gene and isoniazid resistance detection is determined by detecting mutations in the *inhA* promoter region and the *katG* gene. The BD MAX System monitors these signals at each cycle, and interprets the data at the end of the program to report the final results.

REAGENTS AND MATERIALS

REF	Contents	Quantity
443878	**BD MAX™ MDR-TB Master Mix (E6)** *Dried PCR Master Mix containing nucleotides, Target molecular probes (0.006% w/v) and primers (0.01% w/v) and PCR enzyme (3E-14 % w/v).*	24 tests (2 x 12 tubes)
	BD MAX™ MDR-TB Master Mix (E5) *Dried PCR Master Mix containing nucleotides, Target and Sample Processing Control molecular probes (0.006% w/v) and primers (0.008% w/v) and PCR enzyme (3E-14 % w/v).*	24 tests (2 x 12 tubes)
	BD MAX™ MDR-TB Reagent Strips *Unitized Reagent Strips containing Wash buffer with 0.1% v/v of Tween® 20 and 3.8% v/v of Tween 80 (0.75 mL), Elution buffer (0.75 mL), Neutralization buffer with 0.02% v/v of Tween 20 (0.75 mL) and binding solution with 5% v/v of Triton® X-100 (0.75 mL) and disposable pipette tips necessary for specimen processing and DNA extraction.*	24 tests
	BD MAX™ MDR-TB Extraction Tubes (E7) *Dried extraction reagent containing DNA magnetic affinity beads (6.4% w/v), protease reagents (6.7% w/v) and Sample Processing Control.*	24 tests (2 x 12 tubes)
	BD MAX™ MDR-TB Sample Tube	24 tests (2 x12 tubes)
	BD MAX™ Transfer Pipets	25
	Septum Caps	25

EQUIPMENT AND MATERIALS REQUIRED BUT NOT PROVIDED

- BD MAX™ STR (Sample Treatment Reagent) (BD Catalog No. 443806)
- BD MAX™ PCR Cartridges (BD Catalog No. 437519)
- External Controls
- Lab coat and disposable gloves, powder-less
- Biomedical Waste Containers
- Stopwatch or timer

For Raw sputum collection:

- Dry, clean, leak-proof containers for collection of sputum

MATERIALS RECOMMENDED BUT NOT PROVIDED IN THE KIT

- Nephelometer
- Sterile tubes
- Sterile 3–5 mm glass beads
- Culture media (BD MGIT™ broth or 7H9 broth)
- Middlebrook OADC
- 7H10/7H11 Agar Plates
- Phosphate Buffered Saline
- Plate Spreaders
- Vortexer
- BD BBL™ MycoPrep™

WARNINGS AND PRECAUTIONS

Danger

H312 Harmful in contact with skin.
H314 Causes severe skin burns and eye damage.
H315 Causes skin irritation.
H317 May cause an allergic skin reaction.
H319 Causes serious eye irritation.
H334 May cause allergy or asthma symptoms or breathing difficulties if inhaled.
H335 May cause respiratory irritation.
H411 Toxic to aquatic life with long lasting effects.
H412 Harmful to aquatic life with long lasting effects.
P260 Do not breathe dust/fume/gas/mist/vapors/spray.
P261 Avoid breathing dust/fume/gas/mist/vapors/spray.
P264 Wash thoroughly after handling.
P272 Contaminated work clothing should not be allowed out of the workplace.
P273 Avoid release to the environment.
P280 Wear protective gloves/protective clothing/eye protection/face protection.
P285 In case of inadequate ventilation wear respiratory protection.
P301+P330+P331 IF SWALLOWED: Rinse mouth. Do NOT induce vomiting.
P312 Call a POISON CENTER/doctor if you feel unwell.
P303+P361+P353 IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water [or shower].
P363 Wash contaminated clothing before reuse.
P321 Specific treatment (see on this label).
P304+P340 IF INHALED: Remove person to fresh air and keep comfortable for breathing.
P310 Immediately call a POISON CENTER/doctor.
P305+P351+P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P302+P352 IF ON SKIN: Wash with plenty of water/…
P333+P313 If skin irritation or rash occurs: Get medical advice/attention.
P337+P313 If eye irritation persists: Get medical advice/attention.
P391 Collect spillage
P405 Store locked up.
P403+P233 Store in a well-ventilated place. Keep container tightly closed.
P501 Dispose of contents/container to an appropriate treatment and disposal facility in accordance with applicable laws and regulations, and product characteristics at time of disposal.

- The BD MAX MDR-TB assay is for *in vitro* Diagnostic Use.
- For optimal performance, the BD MAX MDR-TB assay should be performed within the laboratory environmental bounds of 18 to 28 °C and the laboratory relative humidity bounds of 20 to 80%.
- The BD MAX MDR-TB assay is for testing raw sputum or concentrated sputum sediments prepared from induced or expectorated sputum.
- Do not use expired reagents and/or materials.
- Do not use the kit if the label that seals the outer box is broken upon arrival.
- Do not use reagents if the protective pouches are open or broken upon arrival.
- Do not use reagents if desiccant is not present or is broken inside reagent pouches.
- Do not remove desiccant from reagent pouches.
- Close protective pouches of reagent promptly with the zip seal after each use. Remove any excess air in the pouches prior to sealing.
- Protect reagents against heat and humidity. Prolonged exposure to humidity may affect product performance.
- Do not use reagents if the foil has been broken or damaged.
- Do not mix reagents from different pouches and/or kits and/or lots.

- Do not interchange or reuse caps once used on a tube containing STR treated samples, as contamination may occur and compromise test results.
- Do not reuse BD MAX Sample Tube.
- Check Unitized Reagent Strips for proper liquid fills (ensure that the liquids are at the bottom of the reagent reservoirs) (refer to Figure 1).
- Check Unitized Reagent Strips to ensure that all pipette tips are present (refer to Figure 1).
- Proceed with caution when using chemical solutions as Master Mix and Extraction tube barcode readability may be altered.
- Good laboratory technique is essential to the proper performance of this assay. Due to the high analytical sensitivity of this test, extreme care should be taken to preserve the purity of all materials and reagents.
- In case where other PCR tests are conducted in the same general areas of the laboratory, care must be taken to ensure that the BD MAX MDR-TB kit, any additional reagents required for testing, and the BD MAX System are not contaminated. Avoid microbial and deoxyribonuclease (DNase) contamination of reagents at all times. Gloves must be changed before manipulating reagents and cartridge.
- To avoid contamination of the environment by amplicons, do not break apart the BD MAX PCR Cartridge after use. The seals in the BD MAX PCR Cartridges are designed to prevent contamination.
- The laboratory should routinely perform environmental monitoring to minimize the risk of cross-contamination.
- Performing the BD MAX MDR-TB outside of the recommended time and temperature ranges recommended for specimen transport and storage may produce invalid results. Assays not performed within specified time and temperature ranges should be repeated.
- Additional controls may be tested according to guidelines or requirements of local, state, provincial and/or federal regulations or accrediting organizations.
- Always handle samples as if they are infectious and in accordance with safe laboratory procedures such as those described in CLSI Document M29[4] and in Biosafety in Microbiological and Biomedical Laboratories.[5]
- Wear protective clothing and disposable gloves while handling all reagents.
- Wash hands thoroughly after performing the test.
- Do not pipette by mouth.
- Do not smoke, drink, chew, or eat in areas where specimens or kit reagents are being handled.
- Dispose of unused reagents and waste in accordance with local, state, provincial and/or federal regulations.
- Consult the BD MAX System User's Manual[8] for additional warnings, precautions, and procedures.

STORAGE AND STABILITY

Collected raw sputum specimens should be kept between 2 °C and 35 °C during transport of up to 3 days. Protect against exposure to excessive heat.

Raw sputum: specimen can be stored for up to an additional 168 hours (7 days) at 2–8 °C before treatment with STR.

Sputum sediment: specimen can be stored for up to 168 hours (7 days) at 2–8 °C before treatment with STR.

BD MAX STR treated samples can be stored at 2–28 °C for a maximum of 72 hours.

Prepared BD MAX MDR-TB Sample Tubes can be stored at 2–28 °C for a maximum of 72 hours post STR treatment.

BD MAX MDR-TB components are stable at 2–28 °C through the stated expiration date. Do not use expired components.

BD MAX MDR-TB Master Mix and Extraction Tubes are provided in sealed pouches. To protect product from humidity, immediately re-seal after opening. Reagent tubes are stable for up to 14 days at 2–28 °C after initial opening and re-sealing of the pouch.

INSTRUCTIONS FOR USE

Specimen Collection/Transport

In order to obtain an adequate specimen, the procedure for specimen collection must be followed closely. All specimens should be collected and transported as recommended by the Centers for Disease Control and Prevention (CDC),[5] the *Clinical Microbiology Procedures Handbook*,[6] or your institution's procedure manual. Patients should be seated or standing for collection of raw sputum. Patients should rinse their mouths of any potential food particles or debris prior to collection of sputum.

Raw sputum or concentrated sputum sediments prepared from induced or expectorated sputa specimens are collected according to the following procedure:

NOTE: Reject samples with obvious food particles or other solid particulates.

1. Raw sputum: Using a leak-proof sputum collection container, collect at least 1 mL of sputum. Label the container and transport to the laboratory (refer to the Storage and Stability section).
2. Sputum sediment: Decontaminate the sputum specimen with NALC/NaOH according to the method of Kent and Kubica.[7] Re-suspend the sediment in up to 2 mL of 67 mM Phosphate/water buffer. Label the container and transport to the laboratory (refer to the Storage and Stability section). A minimum of 1 mL is required for testing with BD MAX MDR-TB.

Specimen Preparation

NOTE: The BD MAX MDR-TB assay can only be used with the BD MAX STR kit. Processing steps for sputum and sputum sediments can be found in the BD MAX STR package insert.

NOTE: One (1) BD MAX STR tube, one (1) Transfer Pipet, one (1) Sample Tube, one (1) Septum Cap, two (2) Master Mix Tubes (one [E6] and one [E5]), one (1) Extraction Tube [E7] and one (1) Unitized Reagent Strip are required for each specimen and each External Control to be tested. Set aside the required number of materials from their protective pouches or boxes. To store opened Master Mix or Extraction Tube pouches, remove excess air and close using the zip seal.

1. Label a barcoded BD MAX MDR-TB Sample Tube (clear cap) with the appropriate specimen identification. Do not obscure, write or label over the 2D-barcode.

   For each raw sputa specimen or sputum sediment: (Steps 2 to 7 describe the use of the BD MAX STR [Not provided]. For further information refer to BD MAX STR package insert.)
2. Allow the sample to equilibrate to room temperature.
3. Carefully open the lid of the leak-proof sputum collection container using caution not to spill.
4. Carefully open BD MAX STR tube and add the required volume so that the final ratio of STR:sample is 2:1.
5. Cap the collection container and shake (do not vortex) the solution vigorously 10 times (up and down equals 1 time).
6. Incubate at room temperature for 5 minutes and shake vigorously again 10 times.
7. Incubate BD MAX STR-treated sample at room temperature for 25 minutes.
8. Remove the cap from the BD MAX MDR-TB Sample Tube and retain the hard cap if storing sample.
9. Using the transfer pipet supplied, transfer 2.5 mL of the STR-treated sputum sample to a labeled BD MAX MDR-TB Sample Tube. Double check that the sample ID on the BD MAX MDR-TB Sample Tube matches the label on collection container.
10. Close the BD MAX MDR-TB Sample Tube with a blue septum cap
11. Prepare any additional specimens for testing by repeating Steps 1 through 10, prior to handling additional specimens.
12. Proceed to BD MAX System Operation section to perform testing of the BD MAX MDR-TB on the BD MAX System.

BD MAX System Operation

NOTE: Refer to the BD MAX System User's Manual[8] for detailed instructions (refer to the Operation section).

NOTE: Testing of the BD MAX MDR-TB kit must be performed immediately following transfer of STR treated specimen to the Sample Tube above (refer to "Specimen Preparation", Step 9).

1. Power on the BD MAX System (if not already done) and log in by entering **<user name>** and **<password>**.
2. Gloves must be changed before manipulating reagents and cartridges.
3. Remove the required number of Unitized Reagent Strips from the BD MAX MDR-TB kit. Gently tap each Unitized Reagent Strip onto a hard surface to ensure that all the liquids are at the bottom of the tubes.
4. Remove from the protective pouches the required number of Extraction Tube(s) and Master Mix Tube(s) from the BD MAX MDR-TB kit.
5. Remove excess air, and close pouches with the zip seal.
6. For each sample to be tested, place one (1) Unitized Reagent Strip on the BD MAX System Rack, starting with Position 1 of Rack A.
7. Snap one (1) Extraction Tube (E7) (white foil) into each Unitized Reagent Strip in Position 1 as shown in Figure 1.
8. Snap one (1) BD MAX MDR-TB Master Mix tube (E6) (green foil) into each Unitized Reagent Strip in Position 2 as shown in Figure 1.
9. Snap one (1) BD MAX MDR-TB Master Mix tube (E5) (blue foil) into each Unitized Reagent Strip in Position 4 as shown in Figure 1.

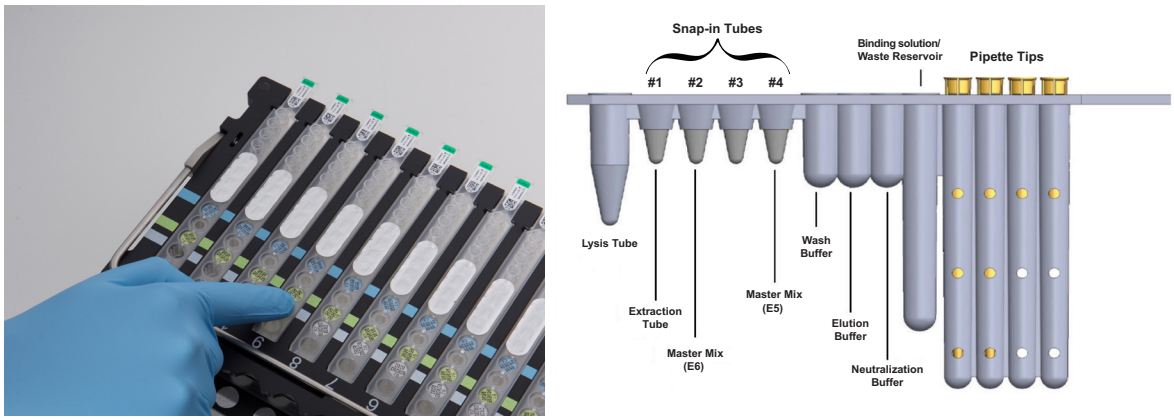

Figure 1: Snap BD MAX MDR-TB Extraction tubes and BD MAX MDR-TB Master Mix tubes into Unitized Reagent Strips

10. Click on the Run icon then Inventory. Enter the kit lot number for the BD MAX MDR-TB kit (for lot traceability) by either scanning the barcode with the scanner or by manual entry (on the outer box).

    NOTE: Repeat step 10 each time a new kit lot is used.

11. Navigate to the Worklist. Using the pull down menu select **<BD MAX MDR TB 70>**.
12. Enter the BD MAX MDR-TB Sample Tube ID, Patient ID and Accession Number (if applicable) into the Worklist, either by scanning the barcode with the scanner or by manual entry.
13. Select the appropriate kit lot number (found on the outer box of the BD MAX MDR-TB kit) from the pull down menu.
14. Repeat steps 11 to 13 for all remaining Sample Tubes.
15. Place the Sample Tubes in the BD MAX System Rack(s) corresponding to the Unitized Reagent Strips assembled in steps 6 to 9.

    NOTE: Place the Sample Tubes into the specimen rack with 1D barcode labels facing outward (this makes scanning Sample Tubes easier during sample login).

16. Place the required number of BD MAX PCR Cartridge(s) into the BD MAX System (refer to Figure 2):
    - Each BD MAX PCR Cartridge accommodates up to 12 samples.
    - The BD MAX System will automatically select the position and row on the BD MAX PCR Cartridge for each run. BD MAX PCR Cartridges may be used multiple times until all lanes have been utilized.
    - To maximize use of BD MAX PCR Cartridges, using 2000 Sample Mode, select Run Wizard under the Worklist tab for lane assignments.
    - Consult the BD MAX System User's Manual[8] for more details.

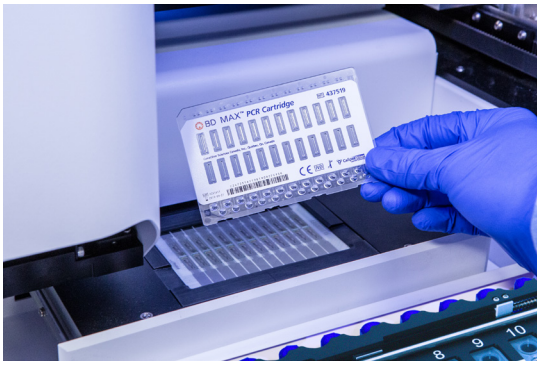

Figure 2: Load BD MAX PCR Cartridges

17. Load rack(s) into the BD MAX System (refer to Figure 3).

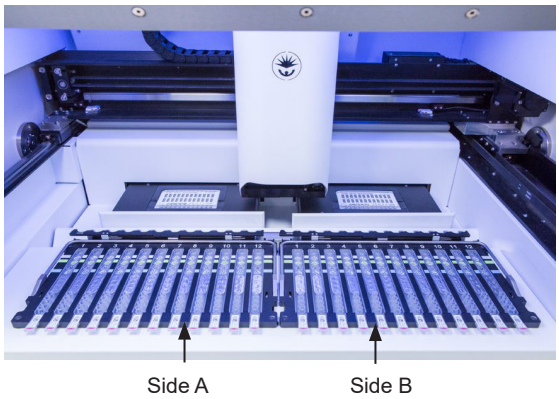

Figure 3: Load Rack(s) into the BD MAX System

18. Close the BD MAX System lid and click **<Start>** to begin processing.
19. A**t the end of the run, check results immediately or store Sample Tubes at 2–28 °C for up to 72 hours post STR treatment until the results are checked.**

    NOTE: Replace septum cap with a hard cap before storing the sample.

    NOTE: Prepared BD MAX MDR-TB Sample Tubes can be stored at 2–28 °C for a maximum of 72 hours. When an Indeterminate (IND), Unresolved (UNR), or Incomplete (INC) result is obtained, or when an External Control failure occurs, a repeat test from the prepared Sample Tube must be performed within this timeframe (refer to Repeat Test Procedure section).

    NOTE: If an external control fails, repeat testing of all specimens using freshly prepared external controls (see Quality Control section).

QUALITY CONTROL

Quality control procedures monitor the performance of the assay. Laboratories must establish the number, type and frequency of testing control materials according to guidelines or requirements of local, provincial, state, federal and/or country regulations or accreditation organizations in order to monitor the effectiveness of the entire analytical process. For general Quality Control guidance, the user may wish to refer to CLSI MM3[9] and EP12.[10]

1. External Control materials are not provided by BD. External Positive and Negative Controls are not used by the BD MAX System software for the purpose of sample test result interpretation. External Controls are treated as if they were patient samples. BD MAX STR is required to prepare External Controls. (Refer to the table in the Results Interpretation section for the interpretation of External Control assay results.)
2. One External Positive Control and one External Negative Control should be run at least daily until adequate process validation is achieved on the BD MAX System in each laboratory setting. Reduced frequency of control testing should be in accordance with applicable regulations.
3. The External Positive Control is intended to monitor for substantial reagent failure. The External Negative Control is used to detect reagent or environmental contamination (or carry-over) by target nucleic acids.
4. Control strains should be tested according to guidelines or requirements of local, state and/or federal regulations or accreditation organizations in order to monitor the effectiveness of the entire analytical process.
5. Various types of External Controls are recommended to allow the user to select the most appropriate for their laboratory quality.
   a. External Negative controls must contain 2.5 mL of STR solution (2 parts STR: 1 part deionized water).
   b. External Positive Control: A suspension of any verified *M. tuberculosis* complex organism acquired commercially or through culture isolation procedures or a previously characterized sample known to be positive.

   If control organisms are used
   a. Grow organism in either 7H9 broth or BD MGIT broth, supplemented with OADC at 37 °C. Grow to an approximate turbidity of ≥0.5 McFarland (typically 7 to 10 days but may be longer depending on strain).
   b. Remove liquid culture by centrifugation for 10 minutes at 3,000 g.
   c. Resuspend the organism in phosphate buffered saline (PBS).
   d. Transfer the suspension to a sterile tube containing up to ten (10) 3–5 mm beads. Vortex the culture for approximately 30 seconds.
   e. Allow the suspension to settle for approximately 5 minutes to allow for bigger particulates to reach the bottom of the tube.
   f. Transfer the suspension to a new sterile tube, avoiding the clumps at the bottom of the tube and ensure turbidity remains ≥0.5 McFarland.
      1) Tube dimensions should be specific for the nephelometer.
   g. Perform serial dilutions and plate the organism onto agar plates (7H10 or 7H11 agar) for quantification. Allow agar plates to incubate at 37 °C for 2 to 4 weeks.
   h. Upon quantification of organism, dilute organism to a concentration of 1 x 10^5 CFU/mL in PBS.
      1) Suspension can be prepared to the final dilution, divided into 300 µL aliquots, frozen and used for routine testing.
   i. Add 2.25 mL of STR solution (2 parts STR: 1 part deionized water) to the sample tube.
   j. Add 250 µL of the final dilution to the BD MAX MDR-TB Sample Tube and recap the tube with a blue septum cap.
   k. Process the External Control as if it is a patient sample according to the procedure indicated in the BD MAX System Operation System section.
6. All External Controls should yield the expected results (positive for External Positive Control, negative for External Negative Control) and no failed external controls (Unresolved or Indeterminate results). See table below for acceptable results for the External Positive Control:

***M. tuberculosis* Organism or Characterized Specimen**	**Assay Result**
RIF Susceptible and INH Susceptible	MTB Detected, RIF Resistance NOT Detected, INH Resistance NOT Detected
RIF Susceptible/INH Resistant	MTB Detected, RIF Resistance NOT Detected, INH Resistance Detected
RIF Resistant/INH Susceptible	MTB Detected, RIF Resistance Detected, INH Resistance NOT Detected
RIF Resistant/INH Resistant	MTB Detected, RIF Resistance Detected, INH Resistance Detected

   a. An External Negative Control that yields a positive test result is indicative of a sample handling and/or contamination event. Review the sample handling technique to avoid mix-up and/or contamination. An External Positive Control that yields a negative result is indicative of a sample handling/preparation problem. Review the sample handling/preparation technique.
   b. An External Control that yields an Unresolved, Indeterminate or Incomplete test result is indicative of a reagent or a BD MAX System failure. Check the BD MAX System monitor for any error messages. Refer to the Troubleshooting section of the BD MAX System User's Manual[8] for interpretation of warning and error codes. If the problem persists, use reagents from an unopened pouch or use new BD MAX MDR-TB kits.

c. Each BD MAX MDR-TB Extraction Tube contains a Sample Processing Control which is a plasmid containing a synthetic target DNA sequence. The Sample Processing Control is extracted, eluted and amplified along with any target DNA present in the processed sample. The Sample Processing Control monitors the efficiency of DNA capture, washing and elution during the sample processing steps, as well as the efficiency of DNA target amplification and detection during PCR analysis. If the Sample Processing Control result fails to meet the acceptance criteria, the result of the sample will be reported as Unresolved; however, any positive MTBC results ("MTB Detected") will be reported. Repeat any sample reported as Unresolved according to the "Repeat Test Procedure" section below.

RESULTS INTERPRETATION

Results are available on the **<Results>** tab in the **<Results>** window on the BD MAX System monitor. The BD MAX System software automatically interprets test results. Results are reported for each of the analytes and for the Sample Processing Control. A test result may be called as MTB Detected, MTB Low POS, MTB NOT Detected, RIF Resistance Detected, RIF Resistance NOT Detected, RIF Resistance UNREPORTABLE, INH Resistance Detected *(katG Mut NOT Detected; katG Mut Detected; inhApr Mut NOT detected; inhApr Mut Detected also reported),* INH Resistance NOT Detected, INH Resistance UNREPORTABLE, or UNR (unresolved) based on the amplification status of the target and of the Sample Processing Control. IND (Indeterminate) or INC (Incomplete) results are due to BD MAX System failure. BD MAX MDR-TB results interpretation is described below in Table 1.

Table 1: BD MAX MDR-TB Assay Result Interpretation

ASSAY RESULT REPORTED		INTERPRETATION OF RESULT
MTB Detected		*Mycobacterium tuberculosis* complex DNA detected
MTB Low POS		*Mycobacterium tuberculosis* complex DNA detected, resistance metrics not measurable; ≥2 *RRDR*[a], *katG* or *inhA* promoter probes failed to give a signal, indicative of low bacterial load
MTB NOT Detected		No *Mycobacterium tuberculosis* complex DNA detected and Sample Processing Control detected
RIF Resistance Detected		Mutation(s) in the *RRDR*[a] were detected
RIF Resistance NOT Detected		No mutation(s) in the *RRDR*[a] were detected
RIF Resistance UNREPORTABLE		*Mycobacterium tuberculosis* complex DNA detected but RIF resistance metrics not measurable; a single *rpoB* probe failed to give a signal with the remaining *rpoB* probes presenting as wild-type signals
INH Resistance Detected[c]	***katG* Mut NOT Detected**	INH resistant DNA was detected; no mutation(s) in the *katG* assay target were detected
	***katG* Mut Detected**	INH resistant DNA was detected; mutation(s) in the *katG* assay target were detected
	***inhApr*[b] Mut NOT Detected**	INH resistant DNA was detected; no mutation(s) in the *inhA* promoter assay target were detected
	***inhApr*[b] Mut Detected**	INH resistant DNA was detected; mutation(s) in the *inhA* promoter assay target were detected
INH Resistance NOT Detected		No mutation(s) in both the *katG* and *inhA* promoter assay targets were detected
INH Resistance UNREPORTABLE		*Mycobacterium tuberculosis* complex DNA detected but INH resistance metrics not measurable; either the *katG* or *inhA* promoter probe failed to give a signal with the other signal presenting as wild type
MTB Unresolved (MTB UNR)		No *Mycobacterium tuberculosis* complex DNA detected and no Sample Processing Control is detected (indicative of an inhibitory sample or reagent failure)
Indeterminate (IND)		Indeterminate due to BD MAX System failure (with Warning or Error Code[d])
Incomplete (INC)		Incomplete Run (with Warning or Error Code[d])

[a]RRDR = Rifampin Resistance Determining Region (81 bp region of the *rpoB* gene, codons 507–533)

[b]*inhApr* = *inhA* promoter region

[c]If either the *katG* or *inhApr* resistance (Mut NOT Detected or Mut Detected) is not reported with the INH Resistance Detected result, then that target call is unreportable. The assay probe for that target failed to give a signal.

[d]Refer to Troubleshooting section of the BD MAX System User's Manual[8] for interpretation of warning and error codes.

REPEAT TEST PROCEDURE

NOTE: Sufficient volume is available for one repeat test from the BD MAX MDR-TB Sample Tube. For prepared BD MAX MDR-TB Sample Tubes stored at 2–28 °C, retesting must be performed within 72 hours following the initial BD MAX STR treatment of the specimen. The remaining STR treated sputa specimen may also be used for repeat testing within 72 hours if stored at 2–28 °C.

NOTE: New samples may be tested in the same run with repeat samples.

MTB Low POS Result

MTB Low POS results are obtained in the event that sample(s) are MTB positive and there is loss of signal for ≥2 resistance target probes, signaling a bacterial load between the limits of detection of the MTB detection and resistance determination assays.

The test may be repeated as described above, however, there is a likelihood that the resistance results will not be reported as the bacterial load in the sample could be below the limits of detection for the RIF and/or INH assays.

Sample(s) can be repeated from their corresponding Sample Tube(s) within the timeframes defined above. Restart from the "BD MAX System Operation" section. The remaining sputa sample may also be used for repeat testing with the preparation of a new Sample Tube within the timeframes defined above. Restart from the Sample Preparation section.

RIF or INH Resistance Unreportable Result

Resistance Unreportable results may be obtained in the event that there is loss of signal for one resistance target probe. The test should be repeated as described above.

Sample(s) can be repeated from their corresponding Sample Tube(s) within the timeframes defined above. Restart from the "BD MAX System Operation" section. The remaining sputa sample may also be used for repeat testing with the preparation of a new Sample Tube within the timeframes defined above. Restart from the Sample Preparation section.

MTB Unresolved Result

MTB Unresolved results may be obtained in the event that sample-associated inhibition or a reagent failure prevents proper target and/or Sample Processing Control amplification. If the Sample Processing Control does not amplify, the sample will be reported as MTB UNR. The test should be repeated as described above.

Sample(s) can be repeated from their corresponding Sample Tube(s) within the timeframes defined above. Restart from the "BD MAX System Operation" section. The remaining STR-treated sample may also be used for repeat testing with the preparation of a new Sample Tube within the timeframes defined above. Restart from the Sample Preparation section.

Indeterminate Result

Indeterminate results may be obtained in the event that a System failure occurs. Sample(s) can be repeated from their corresponding Sample Tube(s) within the timeframes defined above. Restart following the "BD MAX System Operation" section. The remaining STR-treated sample, prepared within a new Sample Tube, may also be used for repeat testing within the timeframe defined above. Restart from the Specimen Preparation section. For the interpretation of warning or error code messages, refer to the BD MAX User's Manual[8] (Troubleshooting section).

Incomplete Result

Incomplete results may be obtained in the event that the Specimen Preparation or the PCR failed to complete. Sample(s) can be repeated from their corresponding Sample Tube(s) within the timeframes defined above. Restart following "BD MAX System Operation" section. The remaining STR-treated sample, prepared in a new Sample Tube, may also be used for repeat testing within the timeframe defined above. Restart from the Specimen Preparation section. For the interpretation of warning or error code messages, refer to the BD MAX System User's Manual[8] (Troubleshooting section).

External Control Failure

External Controls should yield expected results when tested. If samples have to be repeated due to an incorrect External Control result, they should be repeated from their Sample Tubes along with freshly prepared External Controls within the timeframes defined above. Restart following the "BD MAX System Operation" section.

LIMITATIONS OF THE PROCEDURE

- This product should only be used with the BD MAX System by trained laboratory personnel.
- This product is intended for use only with BD MAX STR treated raw sputum or concentrated sputum sediments prepared from induced or expectorated sputa.
- Erroneous results may occur from improper specimen collection, handling, storage, technical error, specimen mix-up or because the number of organisms in the specimen is below the analytical sensitivity of the test.
- If the BD MAX MDR-TB assay result is IND, INC, or UNR then the test should be repeated.
- Interference with the BD MAX MDR-TB assay was observed in the presence of Mucin at levels above 1.5% w/v (Table 24 Performance Characteristics section).
- A BD MAX MDR-TB positive result does not necessarily indicate the presence of viable organisms. It does however indicate the presence of target DNA.
- Mutations or polymorphisms in primer- or probe-binding regions may affect detection of new or unknown target variants, resulting in an incorrect result with the BD MAX MDR-TB assay.
- As with all PCR-based tests, extremely low levels of target below the LoD of the assay may be detected, but results may not be reproducible.
- False negative results may occur due to loss of nucleic acid from inadequate collection, transport or storage of specimens, or due to inadequate bacterial lysis. The Sample Processing Control has been added to the test to aid in the identification of samples that contain inhibitors to PCR amplification and as a control for reagent integrity and of the assay system as a whole. The Sample Processing Control does not indicate if nucleic acid has been lost due to inadequate collection, transport or storage of samples, or whether bacterial cells have been inadequately lysed.
- BD MAX MDR-TB assay results may or may not be affected by concurrent medical therapy, which may reduce the amount of target present.
- This test is a qualitative test and does not provide quantitative values nor indicates the quantity of organisms present.
- The performance of the BD MAX MDR-TB Assay has not been evaluated with samples from pediatric patients.

EXPECTED VALUES

The positivity rate of specimens that are positive for *Mycobacterium tuberculosis* (MTB), rifampin resistance (RIF), and isoniazid (also known as isonicotinyl hydrazide) resistance (INH) depends upon the patient population. Factors include the country of origin. In the BD MAX MDR-TB clinical study (March 2016–August 2017) a total of 761 sputa were collected prospectively from countries known to have a high incidence of TB and MDR-TB cases, then frozen. Each sputum sample was split into two (2) portions, one to be digested via the NALC/NaOH digestion method[7] (processed) and one portion considered the raw specimen (lacking digestion). The BD MAX MDR-TB was performed on both portions. The positivity rate for MTB was calculated on the 635 raw sputa plus the 674 processed sputa that were compliant at the specimen and BD MAX MDR-TB levels with a reportable result (Table 2). The RIF positivity rate was calculated on the 316 raw sputa plus the 334 processed sputa that were compliant at the specimen and BD MAX MDR-TB levels with a reportable result for RIF. The INH positivity rate was obtained from the 327 raw sputa plus the 338 processed sputa compliant at the specimen and BD MAX MDR-TB levels with a reportable result for INH. These samples were obtained from 6 countries.

Table 2: Frozen BD MAX MDR-TB Positivity by Country of Sputum Origin

		MAX Positivity Rate		
Country of Collection	**Specimen Type**	**MTB**	**RIF**	**INH**
Mali	Raw Sputum	43.0% (92/214)	4.2% (3/72)	8.3% (6/72)
	Processed Sputum	41.0% (87/212)	5.6% (4/71)	9.6% (7/73)
Mexico	Raw Sputum	100% (5/5)	0.0% (0/5)	0.0% (0/5)
	Processed Sputum	75.0% (6/8)	0.0% (0/6)	0.0% (0/6)
Republic of Moldova	Raw Sputum	94.3% (82/87)	28.2% (20/71)	43.9% (36/82)
	Processed Sputum	96.6% (84/87)	33.3% (25/75)	43.0% (34/79)
Russia	Raw Sputum	87.5% (14/16)	50.0% (5/10)	36.4% (4/11)
	Processed Sputum	81.3% (13/16)	33.3% (3/9)	40.0% (4/10)
South Africa	Raw Sputum	69.2% (72/104)	0.0% (0/65)	1.6% (1/64)
	Processed Sputum	67.3% (70/104)	1.5% (1/68)	1.6% (1/64)
Uganda	Raw Sputum	51.9% (107/206)	1.1% (1/91)	3.3% (3/91)
	Processed Sputum	53.7% (131/244)	0.0% (0/103)	2.9% (3/104)
Unknown	Raw Sputum	66.7% (2/3)	0.0% (0/2)	0.0% (0/2)
	Processed Sputum	66.7% (2/3)	0.0% (0/2)	0.0% (0/2)
Total	Raw Sputum	58.9% (374/635)	9.2% (29/316)	15.3% (50/327)
	Processed Sputum	58.3% (393/674)	9.9% (33/334)	14.5% (49/338)

In a second BD MAX MDR-TB clinical study (May 2017–March 2018) a total of 1,063 compliant sputa were collected prospectively from countries known to have a high incidence of TB and MDR-TB cases. Each fresh sputum sample was split into two (2) portions, one to be digested via the NALC/NaOH digestion method[7] (processed) and one portion considered the raw specimen (lacking digestion). The BD MAX MDR-TB was performed on both portions. The positivity rate for MTB was calculated on the 953 raw sputa and the 965 processed sputa that were compliant at the specimen and BD MAX MDR-TB levels with a reportable result (Table 3). The RIF positivity rate was calculated on the 255 raw sputa and the 236 processed sputa that were compliant at the specimen and BD MAX MDR-TB levels with a reportable result for RIF. The INH positivity rate was obtained from the 256 raw sputa and the 233 processed sputa compliant at the specimen and BD MAX MDR-TB levels with a reportable result for INH. These samples were obtained from four countries.

Table 3: Fresh BD MAX MDR-TB Positivity by Country of Sputum Origin

		MAX Positivity Rate		
Country of Collection	**Specimen Type**	**MTBC**	**RIF**	**INH**
India	Raw Sputum	42.3% (52/123)	4.4% (2/45)	9.3% (4/43)
	Processed Sputum	43.5% (54/124)	2.5% (1/40)	10.0% (4/40)
Peru	Raw Sputum	49.6% (125/252)	13.1% (16/122)	15.4% (19/123)
	Processed Sputum	49.0% (124/253)	14.5% (17/117)	14.2% (16/113)
South Africa	Raw Sputum	10.4% (33/318)	0.0% (0/22)	0.0% (0/23)
	Processed Sputum	12.1% (39/322)	4.5% (1/22)	5.0% (1/20)
Uganda	Raw Sputum	28.8% (75/260)	3.0% (2/66)	4.5% (3/67)
	Processed Sputum	26.7% (71/266)	3.5% (2/57)	5.0% (3/60)
Total	Raw Sputum	29.9% (285/953)	7.8% (20/255)	10.2% (26/256)
	Processed Sputum	29.8% (288/965)	8.9% (21/236)	10.3% (24/233)

Hypothetical Positive Predictive Value (PPV) and Negative Predictive Value (NPV) were calculated and are represented in Tables 4–6 for MTB, RIF resistance, and INH resistance, respectively. These calculations are based on the hypothetical prevalence and overall sensitivity and specificity obtained compared to the study reference methods.

Table 4: Fresh Hypothetical Positive and Negative Predictive Value for *M. tuberculosis* by Sputum Type

MTBC				PPV		NPV	
MAX Specimen Type	**Prevalence**	**Overall Sensitivity**	**Overall Specificity**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Raw Sputum	1%	92.6% (275/297) (89.0%, 95.1%)	98.6% (584/592) (97.4%, 99.3%)	40.9%	(26.6%, 60.7%)	99.9%	(99.9%, 100%)
	2.5%			63.7%	(47.9%, 79.7%)	99.8%	(99.7%, 99.9%)
	5%			78.3%	(65.3%, 88.9%)	99.6%	(99.4%, 99.7%)
	10%			88.4%	(79.9%, 94.4%)	99.2%	(98.8%, 99.5%)
	15%			92.4%	(86.3%, 96.4%)	98.7%	(98.1%, 99.2%)
	20%			94.5%	(90.0%, 97.5%)	98.2%	(97.3%, 98.8%)
	25%			95.8%	(92.3%, 98.1%)	97.6%	(96.4%, 98.4%)
	30%			96.7%	(93.9%, 98.5%)	96.9%	(95.5%, 98.0%)
	40%			97.9%	(96.0%, 99.0%)	95.2%	(93.1%, 96.9%)
	50%			98.6%	(97.3%, 99.4%)	93.0%	(90.0%, 95.4%)
Processed Sputum	1%	89.2% (263/295) (85.1%, 92.2%)	96.5% (583/604) (94.7%, 97.7%)	20.6%	(14.8%, 28.9%)	99.9%	(99.8%, 99.9%)
	2.5%			39.7%	(30.6%, 50.8%)	99.7%	(99.6%, 99.8%)
	5%			57.4%	(47.5%, 67.9%)	99.4%	(99.2%, 99.6%)
	10%			74.0%	(65.6%, 81.7%)	98.8%	(98.3%, 99.1%)
	15%			81.9%	(75.2%, 87.7%)	98.1%	(97.4%, 98.6%)
	20%			86.5%	(81.1%, 91.0%)	97.3%	(96.3%, 98.1%)
	25%			89.5%	(85.1%, 93.1%)	96.4%	(95.1%, 97.4%)
	30%			91.7%	(88.0%, 94.5%)	95.4%	(93.8%, 96.7%)
	40%			94.5%	(92.0%, 96.4%)	93.0%	(90.7%, 95.0%)
	50%			96.2%	(94.5%, 97.6%)	89.9%	(86.7%, 92.7%)

Table 5: Fresh Hypothetical Positive and Negative Predictive Value for *M. tuberculosis* rifampin resistance (RIF) by Sputum Type

RIF				PPV		NPV	
MAX Specimen Type	**Prevalence**	**Overall Sensitivity**	**Overall Specificity**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Raw Sputum	1%	94.1% (16/17) (73.0%, 99.0%)	98.5% (202/205) (95.8%, 99.5%)	39.4%	(18.9%, 73.9%)	99.9%	(99.7%, 100%)
	2.5%			62.3%	(37.2%, 87.8%)	99.8%	(99.3%, 100%)
	5%			77.2%	(54.8%, 93.6%)	99.7%	(98.5%, 100%)
	10%			87.7%	(71.9%, 96.9%)	99.3%	(96.9%, 100%)
	15%			91.9%	(80.3%, 98.0%)	99.0%	(95.2%, 100%)
	20%			94.1%	(85.2%, 98.6%)	98.5%	(93.3%, 100%)
	25%			95.5%	(88.5%, 98.9%)	98.0%	(91.3%, 99.9%)
	30%			96.5%	(90.8%, 99.2%)	97.5%	(89.0%, 99.9%)
	40%			97.7%	(93.9%, 99.5%)	96.2%	(83.9%, 99.9%)
	50%			98.5%	(95.8%, 99.6%)	94.4%	(77.7%, 99.8%)
Processed Sputum	1%	93.8% (15/16) (71.7%, 98.9%)	97.4% (191/196) (94.2%, 98.9%)	27.1%	(14.2%, 51.3%)	99.9%	(99.7%, 100%)
	2.5%			48.5%	(29.5%, 72.8%)	99.8%	(99.2%, 100%)
	5%			65.9%	(46.2%, 84.6%)	99.7%	(98.4%, 100%)
	10%			80.3%	(64.5%, 92.1%)	99.3%	(96.7%, 100%)
	15%			86.6%	(74.2%, 94.8%)	98.9%	(94.9%, 100%)
	20%			90.2%	(80.3%, 96.3%)	98.4%	(92.9%, 100%)
	25%			92.5%	(84.5%, 97.2%)	97.9%	(90.8%, 99.9%)
	30%			94.0%	(87.5%, 97.8%)	97.3%	(88.5%, 99.9%)
	40%			96.1%	(91.6%, 98.6%)	95.9%	(83.1%, 99.9%)
	50%			97.4%	(94.2%, 99.1%)	94.0%	(76.6%, 99.8%)

Table 6: Fresh Hypothetical Positive and Negative Predictive Value for *M. tuberculosis* isoniazid resistance (INH) by Sputum Type

INH				PPV		NPV	
MAX Specimen Type	**Prevalence**	**Overall Sensitivity**	**Overall Specificity**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Raw Sputum	1%	81.5% (22/27) (63.3%, 91.8%)	100% (205/205) (98.2%, 100%)	100%	(33.9%, 100%)	99.8%	(99.6%, 99.9%)
	2.5%			100%	(56.5%, 100%)	99.5%	(99.0%, 99.8%)
	5%			100%	(72.7%, 100%)	99.0%	(98.0%, 99.7%)
	10%			100%	(84.9%, 100%)	98.0%	(95.9%, 99.3%)
	15%			100%	(89.9%, 100%)	96.8%	(93.7%, 98.9%)
	20%			100%	(92.7%, 100%)	95.6%	(91.3%, 98.4%)
	25%			100%	(94.4%, 100%)	94.2%	(88.7%, 97.9%)
	30%			100%	(95.6%, 100%)	92.6%	(86.0%, 97.4%)
	40%			100%	(97.1%, 100%)	89.0%	(79.8%, 96.0%)
	50%			100%	(98.1%, 100%)	84.4%	(72.4%, 94.1%)
Processed Sputum	1%	84.0% (21/25) (65.3%, 93.6%)	100% (188/188) (98.0%, 100%)	100%	(32.5%, 100%)	99.8%	(99.6%, 100%)
	2.5%			100%	(55.0%, 100%)	99.6%	(99.1%, 99.9%)
	5%			100%	(71.5%, 100%)	99.2%	(98.1%, 99.8%)
	10%			100%	(84.1%, 100%)	98.3%	(96.1%, 99.5%)
	15%			100%	(89.4%, 100%)	97.3%	(94.0%, 99.2%)
	20%			100%	(92.3%, 100%)	96.2%	(91.7%, 98.9%)
	25%			100%	(94.1%, 100%)	94.9%	(89.3%, 98.5%)
	30%			100%	(95.3%, 100%)	93.6%	(86.6%, 98.1%)
	40%			100%	(96.9%, 100%)	90.4%	(80.6%, 97.1%)
	50%			100%	(97.9%, 100%)	86.2%	(73.5%, 95.7%)

PERFORMANCE CHARACTERISTICS

Clinical Performance

Clinical performance characteristics of the BD MAX MDR-TB assay were determined in a multi-site investigational study. The study used prospectively collected, frozen specimens obtained from 761 patients from six countries known to have a high incidence of TB and MDR-TB cases. The study participants were enrolled if they were suspected of having tuberculosis (TB), were at least 18 years old, and either had not received anti-tuberculosis therapy or had received less than three (3) days of therapy in the last six (6) months. Frozen specimens were sent to BD, where they were split randomly and sent to two (2) sites where each sputum sample was split into two (2) portions: one portion was digested via the NALC/NaOH digestive method[7] (processed) and the other portion was considered the raw specimen (lacking digestion). A total of three (3) sites performed the reference method (RM) on the processed sputum, which were fluorescence microscopy (for stratification purposes only), liquid culture followed by Drug Susceptibility Testing (DST), and Cepheid® Xpert MTB/RIF Nucleic Acid Amplification Test (NAAT). For MTB and RIF, either the culture/DST or the NAAT needed to be positive to have a RM positive. Both methods needed to be negative to obtain a negative RM. For INH, only the culture/DST was the RM. Two (2) other sites performed the BD MAX MDR-TB assay on the processed and the raw portions of the specimens. A total of 761 patients provided their sputum specimen. Specimens were excluded from the study due to inaccurate specimen handling and processing, inadequate amount of specimen received, absence of corresponding BD MAX results, and a sputum volume less than 1.5 mL. A total of 643 raw sputa and 678 processed sputa specimens from 686 patients were compliant at the BD MAX MDR-TB level. Of them, 596 raw sputa and 635 processed sputa from 645 patients had also a compliant reference method and were included in the performance characteristics calculations. In total, 384 males, 256 females, and 5 individuals for which the gender was not recorded were included in the performance characteristics. Specimens that gave a non-compliant or missing RM result, or a BD MAX missing result were removed from clinical data calculations. Any initial BD MAX non-reportable result was repeated.

Table 7 summarizes the sensitivity and specificity by specimen type and smear status for MTB. Tables 8 and 9 summarize the sensitivity and specificity by specimen type for RIF and INH resistance.

Table 7: Frozen MTB Sensitivity and Specificity compared to the composite RM (culture plus NAAT)

	Raw Sputum	Processed Sputum
Sensitivity Smear-Positive	98.3% (229/233) (95.7%, 99.3%)	99.2% (245/247) (97.1%, 99.8%)
Sensitivity Smear-Negative	88.5% (131/148) (82.4%, 92.7%)	90.3% (139/154) (84.6%, 94.0%)
Overall Sensitivity	94.5% (360/381) (91.7%, 96.4%)	95.8% (384/401) (93.3%, 97.3%)
Overall Specificity	94.9% (204/215) (91.1%, 97.1%)	97.0% (227/234) (94.0%, 98.5%)

Out of the 360 MTB true positive results with raw sputa, 106 had a RIF Reference method non-evaluable. Among the 254 specimens MTB true positive and with RIF RM evaluable, 15 and 13 specimens had an initial MTB Low POS result and RIF Resistance Unreportable, respectively. Upon valid repeat, 7 and 4 specimens were still MTB Low POS result and RIF Resistance Unreportable, respectively.

Out of the 384 MTB true positive with processed sputa, 118 had a RIF Reference method non-evaluable. Among the 266 specimens MTB true positive and with RIF RM evaluable, 24 and 11 specimens had an initial MTB Low POS result and RIF Resistance Unreportable, respectively. Upon valid repeat, 11 and 2 specimens were still MTB Low POS result and RIF Resistance Unreportable, respectively.

Table 8: Frozen RIF Performance Overall compared to the composite RM (culture/DST plus NAAT)

	Raw Sputum	Processed Sputum
Overall Sensitivity	100% (26/26) (87.1%, 100%)	100% (30/30) (88.6%, 100%)
Overall Specificity	100% (206/206) (98.2%, 100%)	99.1% (214/216) (96.7%, 99.7%)

Out of the 360 MTB true positive results with raw sputa, 107 had an INH Reference method non-evaluable. Among the 253 specimens MTB true positive and with INH RM evaluable, 14 and 2 specimens had an initial MTB Low POS result and INH Resistance Unreportable, respectively. Upon valid repeat, 7 and 0 specimens were still MTB Low POS result and INH Resistance Unreportable, respectively.

Out of the 384 MTB true positive with processed sputa, 115 had an INH Reference method non-evaluable. Among the 269 specimens MTB true positive and with INH RM evaluable, 29 and 3 specimens had an initial MTB Low POS result and INH Resistance Unreportable, respectively. Upon valid repeat, 15 and 2 specimens were still MTB Low POS result and INH Resistance Unreportable, respectively.

Table 9: Frozen INH Performance Overall compared to the RM (culture/DST)

	Raw Sputum	Processed Sputum
Overall Sensitivity	100% (43/43) (91.8%, 100%)	100% (41/41) (91.4%, 100%)
Overall Specificity	100% (199/199) (98.1%, 100%)	100% (209/209) (98.2%, 100%)

A total of 643 raw sputa and 678 processed sputa specimens were based on compliant sputum specimens and BD MAX MDR-TB results. An initial BD MAX MDR-TB non-reportable result was repeated. Table 10 summarizes the MTB Unresolved, the Indeterminate, and the Incomplete results rates by specimen type.

Table 10: Frozen MTB UNR, IND, INC and Combined Non-reportable Rates by Sputum Type

	MTB Unresolved (UNR)		Indeterminate (IND)		Incomplete (INC)		Total Non-Reportable (UNR+IND+INC)	
Specimen Type	Initial (95% CI)	Valid Repeat (95% CI)	Initial (95% CI)	Valid Repeat (95% CI)	Initial (95% CI)	Valid Repeat (95% CI)	Initial (95% CI)	Valid Repeat (95% CI)
Raw Sputum	2.5% (16/643) (1.5%, 4.0%)	0.2% (1/636) (0.0%, 0.9%)	3.1% (20/643) (2.0%, 4.8%)	0.0% (0/636) (0.0%, 0.6%)	0.0% (0/643) (0.0%, 0.6%)	0.0% (0/636) (0.0%, 0.6%)	5.6% (36/643) (4.1%, 7.7%)	0.2% (1/636) (0.0%, 0.9%)
Processed Sputum	0.7% (5/678) (0.3%, 1.7%)	0.0% (0/674) (0.0%, 0.6%)	1.2% (8/678) (0.6%, 2.3%)	0.0% (0/674) (0.0%, 0.6%)	0.0% (0/678) (0.0%, 0.6%)	0.0% (0/674) (0.0%, 0.6%)	1.9% (13/678) (1.1%, 3.3%)	0.0% (0/674) (0.0%, 0.6%)

Clinical performance characteristics of the BD MAX MDR-TB assay were determined in a second multi-site investigational study. The study used prospectively collected, fresh specimens from four countries known to have a high incidence of TB and MDR-TB cases. The study participants were enrolled in the case detection group if they were suspected of having tuberculosis (TB), were at least 18 years old, and either had not received anti-tuberculosis therapy or had received less than three (3) days of therapy in the last six (6) months. The study participants were enrolled in the drug-resistant TB group if they were suspected of having tuberculosis (TB), were at least 18 years old and met at least one of the following criteria: i) known pulmonary TB, with suspected treatment failure, ii) history of drug resistant-TB and of anti-TB treatment for 3 months or more, iii) microbiology-confirmed pulmonary TB with documented RIF-resistance who had received anti-TB treatment for 31 days or less.

Performance characteristics for MTB were determined from the case detection group population only. For RIF and INH resistance performance characteristics determination, both populations were combined. Each fresh sputum sample was split into two (2) portions: one portion was digested via the NALC/NaOH digestive method[7] (processed) and the other portion was considered the raw specimen (lacking digestion). Each of the four (4) sites performed the BD MAX MDR-TB assay on the processed and the raw portions of the specimens and the reference method (RM) on the processed sputum, which were liquid culture followed by Drug Susceptibility Testing (DST) and Cepheid Xpert MTB/RIF Nucleic Acid Amplification Test (NAAT). Bi-directional sequencing of a region of the *rpoB* gene was performed by BD to confirm the RIF resistance detected results by the NAAT. For MTB, either the culture or the NAAT needed to be positive to have a RM positive. Both methods needed to be negative to obtain a negative RM. For RIF resistance, either the DST or the NAAT followed by bi-directional sequencing needed to be positive to have a RM positive. Both methods needed to be negative to obtain a negative RM. For INH, only the culture/DST was the RM. Ziehl-Neelsen and Auramine-O stains were performed on raw and processed portions.

A total of 1,091 and 11 subjects were enrolled in the study in the case detection group and the drug-resistant TB group, respectively. Of those, 1,076 and 10 subjects were compliant for the case detection group and the drug-resistant TB group, respectively as per protocol criteria. A total of 1,053 and 10 patients in the case detection group and the drug-resistant TB group, respectively provided a compliant sputum specimen. Specimens were excluded from the study due to inaccurate specimen handling and processing, inadequate amount of specimen received, absence of corresponding BD MAX results, and a specimen too old for testing. A total of 1,033 and raw sputa and 1,034 processed sputa specimens were compliant at the BD MAX MDR-TB level. Of them, 889 raw sputa and 899 processed sputa from 911 patients were included in the performance characteristics calculations. Four hundred eighty-nine (489) males and four hundred twenty-two (422) females were included in the performance characteristics. Specimens that gave a non-compliant or missing RM result, or a BD MAX missing result were removed from clinical data calculations. Any initial BD MAX non-reportable result was repeated.

Table 11 summarizes the prevalence obtained for each target by country.

Table 11: Fresh Prevalence of MTB, RIF and INH resistance by country

	RM Prevalence					
Country of Collection	MTB	RIF	INH	RIF-Resistant Only (INH Susceptible)[a]	INH-Resistant Only (RIF Susceptible)[a]	RIF-Resistant and INH-Resistant[a]
India	43.6% (58/133)	4.9% (2/41)	14.0% (7/50)	0.0% (0/41)	9.8% (4/41)	4.9% (2/41)
Peru	56.6% (151/267)	11.5% (15/130)	15.6% (22/141)	3.1% (4/129)	7.8% (10/129)	7.8% (10/129)
South Africa	10.6% (34/320)	3.8% (1/26)	3.4% (1/29)	0.0% (0/26)	0.0% (0/26)	3.8% (1/26)
Uganda	33.7% (88/261)	2.9% (2/68)	3.9% (3/77)	2.9% (2/68)	4.4% (3/68)	0.0% (0/68)
Total	33.7% (331/981)	7.5% (20/265)	11.1% (33/297)	2.3% (6/264)	6.4% (17/264)	4.9% (13/264)

[a]The denominator is all the specimens that have a reportable POS/NEG result for both the composite RIF RM (culture/DST plus NAAT and bi-directional sequencing) and the INH RM (culture/DST).

Tables 12 and 13 summarize the performance of MTB stratified by Auramine O and Ziehl-Neelsen Staining Methods when the method was performed from the raw and the processed sputum, respectively.

Table 12: Fresh MTB Sensitivity Stratified by Auramine O and Ziehl-Neelsen Staining Methods when the Staining Method was Performed from the Raw Sputum

Staining Methods Performed from the Raw Sputum	Auramine O Method[a]		Ziehl-Neelsen Method[b]	
	BD MAX MDR-TB Assay Performed on		BD MAX MDR-TB Assay Performed on	
	Raw Sputum	Processed Sputum	Raw Sputum	Processed Sputum
	Percent (95% CI)	Percent (95% CI)	Percent (95% CI)	Percent (95% CI)
Sensitivity Smear Pos	100% (178/178) (97.9%, 100%)	100% (176/176) (97.9%, 100%)	100% (149/149) (97.5%, 100%)	100% (147/147) (97.5%, 100%)
Sensitivity Smear Neg	81.5% (97/119) (73.6%, 87.5%)	73.1% (87/119) (64.5%, 80.3%)	85.1% (126/148) (78.5%, 90.0%)	78.4% (116/148) (71.1%, 84.2%)

[a]Smear results were not available for 3 specimens with a Reference Method negative.

[b]Smear results were not available for 2 specimens with a Reference Method negative.

Table 13: Fresh MTB Sensitivity Stratified by Auramine O and Ziehl-Neelsen Staining Methods when the Staining Method was Performed from the Processed Sputum

Staining Methods Performed from the Processed Sputum	Auramine O Method[a]		Ziehl-Neelsen Method[b]	
	BD MAX MDR-TB Assay Performed on		BD MAX MDR-TB Assay Performed on	
	Raw Sputum	Processed Sputum	Raw Sputum	Processed Sputum
	Percent (95% CI)	Percent (95% CI)	Percent (95% CI)	Percent (95% CI)
Sensitivity Smear Pos	99.1% (214/216) (96.7%, 99.7%)	99.5% (213/214) (97.4%, 99.9%)	99.5% (193/194) (97.1%, 99.9%)	99.5% (191/192) (97.1%, 99.9%)
Sensitivity Smear Neg	75.3% (61/81) (64.9%, 83.4%)	61.7% (50/81) (50.8%, 71.6%)	79.6% (82/103) (70.8%, 86.3%)	69.9% (72/103) (60.5%, 77.9%)

[a]Smear results were not available for 2 specimens with a Reference Method negative.

[b]Smear results were not available for 3 specimens with a Reference Method negative.

Table 14 summarizes the sensitivity and specificity by specimen type and collection test sites for MTB. Tables 15 and 16 summarize the sensitivity and specificity by specimen type for RIF and INH resistance.

Table 14: Fresh MTB Sensitivity and Specificity compared to the composite RM (culture plus NAAT)

Site	Raw Sputum		Processed Sputum	
	Sensitivity	Specificity	Sensitivity	Specificity
	Percent (95% CI)	Percent (95% CI)	Percent (95% CI)	Percent (95% CI)
South Africa	91.2% (31/34) (77.0%, 97.0%)	99.3% (265/267) (97.3%, 99.8%)	84.8% (28/33) (69.1%, 93.3%)	95.9% (260/271) (92.9%, 97.7%)
Uganda	92.2% (71/77) (84.0%, 96.4%)	98.7% (148/150) (95.3%, 99.6%)	87.0% (67/77) (77.7%, 92.8%)	98.7% (153/155) (95.4%, 99.6%)
India	98.0% (49/50) (89.5%, 99.6%)	95.6% (65/68) (87.8%, 98.5%)	92.0% (46/50) (81.2%, 96.8%)	91.3% (63/69) (82.3%, 96.0%)
Peru	91.2% (124/136) (85.2%, 94.9%)	99.1% (106/107) (94.9%, 99.8%)	90.4% (122/135) (84.2%, 94.3%)	98.2% (107/109) (93.6%, 99.5%)
Overall	92.6% (275/297) (89.0%, 95.1%)	98.6% (584/592) (97.4%, 99.3%)	89.2% (263/295) (85.1%, 92.2%)	96.5% (583/604) (94.7%, 97.7%)

Out of the 275 plus 3 MTB true positive results with raw sputa from case detection group and resistance group, 44 had a RIF composite reference method non-evaluable. Among the 234 specimens MTB true positive and RIF RM evaluable, 16 and 3 specimens had an initial MTB Low POS result and RIF Resistance Unreportable, respectively. Upon valid repeat, 9 and 2 specimens were still MTB Low POS result and RIF Resistance Unreportable, respectively.

Out of the 263 plus 3 MTB true positive results with processed sputa from case detection group and resistance group, 36 had a RIF composite reference method non-evaluable. Among the 230 specimens MTB true positive and RIF RM evaluable, 28 and 4 specimens had an initial MTB Low POS result and RIF Resistance Unreportable, respectively. Upon valid repeat, 13 and 1 specimens were still MTB Low POS result and RIF Resistance Unreportable, respectively.

Table 15: Fresh RIF Performance Overall compared to the composite RM Culture/DST Plus NAAT and Bi-directional Sequencing

	Raw Sputum	Processed Sputum
Overall Sensitivity	94.1% (16/17)[a] (73%, 99%)	93.8% (15/16)[b] (71.7%, 98.9%)
Overall Specificity	98.5% (202/205) (95.8%, 99.5%)	97.4% (191/196) (94.2%, 98.9%)

[a]Out of the 17 RIF resistant samples, 7 were DST RIF susceptible or non-evaluable, but Xpert MTB/RIF was RIF resistance detected and bi-directional sequencing confirmed the resistance. The resistance detected were L511P, D516Y, D516F, H526N, and L533P.

[b]Out of the 16 RIF resistant samples, 6 were DST RIF susceptible, but Xpert MTB/RIF was RIF resistance detected and bi-directional sequencing confirmed the resistance. The resistance detected were L511P, D516Y, D516F, and L533P.

Out of the 275 plus 3 MTBC true positive results with raw sputa from case detection group and resistance group, 26 had an INH reference method non-evaluable. Among the 252 specimens MTBC true positive and INH RM evaluable, 22 and 8 specimens had an initial MTBC Low POS result and INH Resistance Unreportable, respectively. Upon valid repeat, 17 and 2 specimens were still MTBC Low POS result and INH Resistance Unreportable, respectively.

Out of the 263 plus 3 MTB true positive results with processed sputa from case detection group and resistance group, 23 had a INH reference method non-evaluable. Among the 243 specimens MTB true positive and INH RM evaluable, 35 and 12 specimens had an initial MTB Low POS result and INH Resistance Unreportable, respectively. Upon valid repeat, 19 and 10 specimens were still MTB Low POS result and INH Resistance Unreportable, respectively.

Table 16: Fresh INH Performance Overall compared to the RM (culture/DST)

	Raw Sputum	Processed Sputum
Overall Sensitivity	81.5% (22/27) (63.3%, 91.8%)	84% (21/25) (65.3%, 93.6%)
Overall Specificity	100% (205/205) (98.2%, 100%)	100% (188/188) (98%, 100%)

A total of 1,033 raw sputa and 1,034 processed sputa specimens were based on compliant sputum specimens and BD MAX MDR-TB results. An initial BD MAX MDR-TB non-reportable result was repeated. Table 17 summarizes the MTB Unresolved, the Indeterminate, and the Incomplete results rates by specimen type.

Table 17: Fresh MTB UNR, IND, INC and Total Non-reportable Rate by Sputum Type

	MTB Unresolved (UNR)		Indeterminate (IND)		Incomplete (INC)		Total Non-Reportable (UNR+IND+INC)	
Specimen Type	Initial (95% CI)	Valid Repeat (95% CI)	Initial (95% CI)	Valid Repeat (95% CI)	Initial (95% CI)	Valid Repeat (95% CI)	Initial (95% CI)	Valid Repeat (95% CI)
Raw Sputum	3.8% (39/1,033) (2.8%, 5.1%)	1.0% (10/1,020) (0.5%, 1.8%)	2.8% (29/1,033) (2.0%, 4.0%)	0.6% (6/1,020) (0.3%, 1.3%)	0.6% (6/1,033) (0.3%, 1.3%)	0.6% (6/1,020) (0.3%, 1.3%)	7.2% (74/1,033) (5.7%, 8.9%)	2.2% (22/1,020) (1.4%, 3.2%)
Processed Sputum	2.7% (28/1,034) (1.9%, 3.9%)	0.3% (3/1,022) (0.1%, 0.9%)	1.3% (13/1,034) (0.7%, 2.1%)	0.1% (1/1,022) (0.0%, 0.6%)	0.7% (7/1,034) (0.3%, 1.4%)	0.4% (4/1,022) (0.2%, 1.0%)	4.6% (48/1,034) (3.5%, 6.1%)	0.8% (8/1,022) (0.4%, 1.5%)

Analytical Inclusivity

A variety of BD MAX TB-MDR assay target strains were included in this study. Strain selection criteria included rifampin and isoniazid susceptible and resistance isolates from different geographic locations. A combination of quantitated organisms, thermal cell lysates (acquired from the Belgian Coordinated Collections of Microorganisms/Institute of Tropical Medicine (BCCM/ITM) public collection), and genomic DNA were included in this study. Forty-four (44) well characterized *M. tuberculosis* strains were tested for RIF/INH detection with the BD MAX MDR-TB assay (Table 18 and 19). The strains tested for *M. tuberculosis* complex species inclusivity were; *M. africanum*, *M. bovis*, *M. caprae*, *M. cannetti*, *M. microti*, *M. pinnipedii* (Table 20).

Table 18: Resistance Testing with BD MAX MDR-TB Assay with Thermal Cell Lysates

		Rifampin Resistance[a]		Isoniazid Resistance[b]			
Strain ID	**Origin**	**R/S**	**RRDR Codon**	**R/S**	***katG* Codon**	***inhApr* nucelotide**	**BD MAX MDR-TB Result**
041679	Nepal	R	Ser512Gly Ser531Trp	R	Ser315Thr	WT	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected
971524	Bangladesh	R	Met515Ile Asp516Tyr	S	WT	WT	RIF Resistance Detected
980166	Bangladesh	R	Ser509Arg His526Arg	S	WT	WT	RIF Resistance Detected
970472	Bangladesh	S	WT	R	Ser315Ile	WT	INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected
041204	South Korea	R	Asp516Val	R	WT	C-15T	RIF and INH Resistance Detected *katG* Mut NOT Detected *inhApr* Mut Detected
041207	South Korea	R	Ser531Leu	R	WT	G-9A	RIF and INH Resistance Detected *katG* Mut NOT Detected *inhApr* Mut Detected
041226	South Korea	R	Leu511 Pro	R	Ser315Thr	WT	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* NOT Detected
041203	South Korea	S	WT	R	Ser315Thr	WT	INH Resistance Detected *katG* Mut Detected *inhApr* NOT Detected
042763	Philippines	R	Ser531Leu	R	WT	C-15T	RIF and INH Resistance Detected *katG* Mut NOT Detected *inhApr* Mut Detected
000440	Kazakhstan	R	Ser531Trp	R	Ser315Thr	WT	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* NOT Detected
020115	Georgia	S	WT	R	WT	C-15T	INH Resistance Detected *katG* Mut NOT Detected *inhApr* Mut Detected
042928	Spain	S	WT	R	Ser315Asn	WT	INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected
041668	Germany	S	WT	R	Ser315Thr	C-15T	INH Resistance Detected *katG* Mut Detected *inhApr* Mut Detected
992092	France	R	Ser531Leu	R	Ser315Thr	WT	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected
041655	Bolivia	R	Ser531Leu	R	Ser315Asn	WT	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected
041290	Brazil	S	WT	R	Ser315Thr	WT	INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected
041281	Brazil	R	Asp516Val	S	Ser315Ser	WT	RIF AND INH Resistance Detected[c] *katG* Mut Detected *inhApr* Mut NOT Detected

		Rifampin Resistance[a]		Isoniazid Resistance[b]			
Strain ID	**Origin**	**R/S**	**RRDR Codon**	**R/S**	***katG* Codon**	***inhApr* nucelotide**	**BD MAX MDR-TB Result**
041289	Brazil	R	His526Arg	R	Ser315Thr	C-15T	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* Mut Detected
042611	Peru	R	His526Arg	R	Ser315Asn	WT	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected
040850	South Africa	R	Leu533Pro	R	Ser315Thr	T-8G	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* Mut Detected
041086	Rwanda	R	Ser531Leu	R	Ser315Thr	C-15T	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* Mut Detected
991451	Congo	R	Asp516Tyr	R	Ser315Thr	WT	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected
021555	Burundi	S	WT	R	Ser315Thr	WT	INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected

[a]R= Rifampin Resistant, S= Rifampin Sensitive, WT= wild-type, no nucleotide or codon change

[b]R= Isoniazid Resistant, S= Isoniazid Sensitive, WT= wild-type, no nucleotide or codon change

[c]Phenotypically INH Susceptible but INH resistant by DNA sequence and BD MAX MDR-TB

Table 19: Resistance Testing with BD MAXTM MDR-TB Assay with BD Mycobacterium Repository Isolates

	Rifampicin Resistance		Isoniazid Resistance			
Strain ID	**R/S**	**RRDR Codon**	**R/S**	***katG* Codon**	***inhApr* nucelotide**	**BD MAX MDR-TB Result**
TB006	R	Gln513Lys	R	WT	C-15T	RIF and INH Resistance Detected *katG* Mut NOT Detected *inhApr* Mut Detected
TB007	R	Gln513Lys	R	WT	C-15T	RIF and INH Resistance Detected *katG* Mut NOT Detected *inhApr* Mut Detected
TB009	R	Gln513Lys	S	WT	WT	RIF Resistance Detected
TB010	R	Ser531Leu	R	Ser315Thr	WT	RIF[c] and INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected
TB012[a]	R	His526Tyr	R	Ser315Thr	WT	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected
TB022	R	His526Tyr	S	WT	WT	RIF Resistance Detected
TB023	R	Asp516Tyr	R	Ser315Thr	WT	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected
TB028	R	His526Tyr	R	Ser315Thr	C-15T	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* Mut Detected
TB037	R	Asp516Val	R	Ser315Thr	WT	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected
TB041	R	His526Asp	S	WT	WT	RIF Resistance Detected
TB047	R	deletion codon 519 (AAC)	S	WT	WT	RIF Resistance Detected
TB049	R	Asp516Val	S	WT	WT	RIF Resistance Detected, INH Resistance Unreportable[b]
TB053	R	Ser531Leu	R	Ser315Thr	WT	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected

	Rifampicin Resistance		Isoniazid Resistance			
Strain ID	**R/S**	**RRDR Codon**	**R/S**	***katG* Codon**	***inhApr* nucelotide**	**BD MAX MDR-TB Result**
TB058	R	Asp516Val	R	Ser315Thr	WT	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected
TB059	R	His526Asp	R	Ser315Thr	WT	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected
TB062	R	His526Arg	S	WT	WT	RIF Resistance Detected
TB063	R	Gln513Glu	R	Ser315Thr	WT	RIF and INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected
TB094	R	Leu511Pro Ser512Thr	S	WT	WT	RIF Resistance Detected
TB112	R	His526Leu	R	Ser315Thr	WT	RIF Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected
TB121	S	WT	R	Ser315Asn	C-15T	INH Resistance Detected *katG* Mut Detected *inhApr* Mut Detected
TB123	S	WT	R	Ser315Thr	WT	INH Resistance Detected *katG* Mut Detected *inhApr* Mut NOT Detected

[a]Genomic DNA

[b]Phenotypically INH Susceptible, but INH Unreportable by DNA sequence and BD MAX MDR-TB.

[c]20% of test replicates were RIF unreportable for isolate TB010 at the tested concentration. The Ser531Leu mutation was successfully detected in isolate TB053, therefore TB010 was not tested at higher concentrations.

Table 20: *M. tuberculosis* Inclusivity

MTB Complex Organism	Strain ID
Mycobacterium africanum	ATCC® 25420
Mycobacterium bovis	ATCC TMC 407
Mycobacterium canettiia	BCCM/ITM C02321
Mycobacterium caprae[b]	ATCC BAA-824D-2
Mycobacterium microti	ATCC 35782
Mycobacterium pinnipedii[a]	BCCM/ITM 2015-00021

[a]Thermal Cell Lysate

[b]Genomic DNA

Analytical Sensitivity

The analytical sensitivity (Limit of Detection or LoD) for the BD MAX MDR-TB assay was determined as follows: Isolates of *M. tuberculosis* and *M. bovis* BCG (Bacillus Calmette-Guérin) organism were prepared and quantified prior to inclusion in this study. Organisms were transferred to a sample tube already containing STR treated sputum or sputum pellet that was pre-determined to be negative for all the targets detected by the BD MAX MDR-TB assay. A putative LoD was assessed for each organism tested with a minimum of 36 replicates per sample type (sputum or sputum pellet), using 3 different production lots of the BD MAX MDR-TB assay. The LoD for a specific organism was confirmed by testing at least 20 additional replicates at the determined LoD concentration. Analytical sensitivity (LoD), defined as the lowest concentration at which greater than or equal to 95% of all replicates are expected to test positive (refer to Table 21).

Table 21: Limit of Detection by the BD MAX MDR-TB

Microorganism (strain)	Claimed LoD	Sputum (CFU/mL)	Sputum Pellet (CFU/mL)
M. bovis (BCG)	MTBC	0.5	20
	Resistance	3.75	
M. tuberculosis (H37Rv)	MTBC	0.25	
	Resistance	6.0	

Analytical Specificity (Cross-Reactivity and Exclusivity)

The BD MAX MDR-TB assay was performed on samples containing phylogenetically related species and other organisms (bacteria, viruses, and yeast) likely to be found in sputa specimens. The bacterial cells and yeasts, were tested in the Sample Buffer Tube at ≥1 x 10^6 cells/mL or CFU/mL and *Chlamydia* at >1 x 10^6 EB/mL, in STR treated human sputa. Virus, bacteria, or yeast species not easily acquired underwent *in silico* analysis with each MDR-TB assay target. Overall, 114 organisms were tested and are listed in Table 22. Organisms that underwent *in silico* analysis are listed in Table 23. All of the bacterial strains and yeast tested produced negative results with the BD MAX MDR-TB assay.

Table 22: BD MAX MDR-TB Specificity Results (Bacteria, Yeasts, and Viruses)

Organism		
Actinomyces israelii	*Escherichia coli*	*Mycobacterium scrofulaceum*
Acinetobacter baumannii	*Escherichia coli* producing CTX-M-15 ESBL	*Mycobacterium simiae*
Acinetobacter calcoaceticus	*Fuseobacterium nucleatum*	*Mycobacterium smegmatis*
Actinomyces odontolyticus	*Haemophilus influenzae*	*Mycobacterium szulgai*
Bacteroides fragilis	*Haemophilus parainfluenzae*	*Mycobacterium terrae*
Bacillus cereus	*Haemophilus parahaemolyticus*	*Mycobacterium thermoresistibile*
Bacillus subtilis	*Kingella kingae*	*Mycobacterium triviale*
Bordetella parapertussi	*Klebsiella pneumoniae*	*Mycobacterium xenopi*
Burkholderia cepacia	*Klebsiella oxytoca*	*Mycobacterium ulcerans*
Campylobacter jejuni	*Lactobacillus acidophilus*	*Neisseria gonorrheae*
Candida albicans	*Legionella pneumophilia*	*Neisseria mucosa*
Candida glabrata	*Legionella micdadei*	*Neisseria meningitidis*
Candida krusei	*Leuconostoc mesenteroides*	*Neisseria lactamica*
Candida parapsilosis	*Listeria monocytogenes*	*Neisseria sicca*
Candida tropicalis	*Morganella morganii*	*Pasteurella multocida*
Chlamydia trachomatis Serovar H	*Mycobacterium asiaticum*	*Pediococcus pentosaceus*
Citrobacter freundii	*Mycobacterium avium*	*Peptostreptococcus anaerobius*
Clostridium perfringens	*Mycobacterium celatum*	*Proteus mirabilis*
Corynebacterium pseudodiphtheriticum	*Mycobacterium chelonae*	*Proteus vulgaris*
Corynebacterium jeikeium	*Mycobacterium fortuitum*	*Pseudomonas aeruginosa*
Corynebacterium diptheriae	*Mycobacterium gastri*	*Porphyromonas asaccharolytica*
Corynebacterium xerosis	*Mycobacterium gordonae*	*Prevotella melaninogenica*
Cryptococcus neoformans	*Mycobacterium intracellulare*	*Propionibacterium acnes*
Eikenella corrodens	*Mycobacterium kansasii*	*Providencia stuartii*
Enterobacter aerogenes	*Mycobacterium phlei*	*Rhodococcus equi*
Enterobacter cloacae	*Mycobacterium genavense*	*Salmonella enterica*
Enterococcus avium	*Mycobacterium malmoense*	*Serratia marcescens*
Enterococcus faecalis	*Mycobacterium marinum*	*Shigella flexneri*
Enterococcus faecium	*Mycobacterium mucogenicum*	*Shigella sonnei*

Organism		
Staphylococcus aureus	*Streptococcus equinus*	*Streptococcus uberis*
Staphylococcus capitis	*Streptococcus gallolyticus*	*Streptococcus vestibularis*
Staphylococcus epidermidis	*Streptococcus gordonii*	*Veillonella parvula*
Staphylococcus haemolyticus	*Streptococcus mitis*	*Weissella paramesenteroides*
Staphylococcus hominis	*Streptococcus mutans*	*Yersinia enterocolitica*
Staphylococcus lugdunensis	*Streptococcus oralis*	
Stenotrophomonas maltophilia	*Streptococcus parasanguinis*	
Streptococcus agalactiae	*Streptococcus pneumoniae*	
Streptococcus criceti	*Streptococcus pyogenes*	
Streptococcus constellatus	*Streptococcus salivarius*	
Streptococcus equi	*Streptococcus sanguinis*	

Table 23: BD MAX MDR-TB *in-silico* analysis

Organism	
Adenovirus	*Moraxella catarrhalis*
Human Immunodeficiency Virus	*Mycoplasma pneumoniae*
Human Influenza Virus (Type A)	*Mycobacterium abscessus*
Human Influenza Virus (Type B)	*Mycobacterium flavescens*
Human Metapneumovirus	*Mycobacterium kumamotonense*
Human Parainfluenza Virus Type 1	*Mycobacterium leprae*
Human Parainfluenza Virus Type 2	*Mycobacterium obuense*[a]
Human Parainfluenza Virus Type 3	*M. shimoidei*[a]
Human Parainfluenza Virus Type 4	*Nocardia farcinica*
Mumps Virus	*Nocardia brasiliensis*
Respiratory Syncytial Virus	*Nocardia otitidiscaviarum*
Rhinovirus	*Penicillium* spp.
Rubella Virus	*Rhizopus* spp.
Rubeola Virus	*Scedosporium* spp.
Varicella Zoster Virus	*Stenotrophomonas maltophilia*
Aspergillus fumigatus	*Streptomyces anulatus*
Blastomyces dermatitidis	*Tsukamurella* spp.
Histoplasma capsulatum	

[a]The primers required for amplification of the target DNA in *M. obuense* and *M. shimoidei* also have several base pair mismatches, reducing the amplification efficiency of these targets.

Interfering Substances

Thirty-four (34) biological and chemical substances that may occasionally be present in human sputa were evaluated for potential interference with the BD MAX MDR-TB assay. Substances were tested at levels described in Table 24 below, both in the presence and absence of *M. bovis* BCG at 2x MTBC LoD. Of the 34 substances tested, only one substance, 5% mucin, demonstrated assay inhibition. When mucin was diluted to 1.5% the inhibition was no longer seen. No other reportable interference was observed with the other substances tested (refer to Table 24).

Table 24: Endogenous and Exogenous Substances Tested with the BD MAX MDR-TB

Substance	Result	Substance	Result
Lidocaine (12 µg/mL)	NI	Phenylephrine (50% v/v)	NI
Mupirocin (5% w/v)	NI	Oxymetazoline (20% v/v)	NI
Streptomycin (25 µg/mL)	NI	Sodium chloride nasal spray (100%)	NI
Zanamivir (10 mg/mL)	NI	NaCl (5% w/v)	NI
Human Blood (40% v/v)	NI	Benzocaine (5% w/v)	NI
Gastric Acid (100%)	NI	Guaifenesin (5 mg/mL)	NI
Human DNA (1.0E+6 cells/mL)	NI	Cetylpyridinium Chloride (0.5%)	NI
Human White blood cells (100% buffy coat)	NI	Nicotine (4 µg/mL)	NI

Substance	Result	Substance	Result
Mucin (5%)	I[a]	Tobramycin (24 µg/mL)	NI
Listerine (20% v/v)	NI	Amoxicillin (75.2 µg/mL)	NI
Epinephrine (1 mg/mL)	NI	Levofloxacin (5 mg/mL)	NI
Tea Tree Oil (1% v/v)	NI	Pentamidine (300 ng/mL)	NI
Goldenseal (100%)	NI	Isoniazid (50 µg/mL)	NI
Albuterol sulfate (100 µg/mL)	NI	Rifampin (120 µg/mL)	NI
Budesonide (12.8 µg/mL)	NI	Pyrazinamide (500 µg/mL)	NI
Fluticasone (5 µg/mL)	NI	Ethambutol (60 µg/mL)	NI
Zicam (1 swab/1.67 mL sputa sample)	NI	Streptomycin (25 µg/mL)	NI

NI: No reportable interference with the BD MAX MDR-TB assay.

I: Reportable Interference with the BD MAX MDR-TB assay.

[a]1.5% w/v maximum concentration where interference was not observed.

Mixed Infection–Competitive Interference

The mixed infection/competitive interference study was designed to evaluate the ability of the BD MAX MDR-TB assay to detect low positive results in the presence of non-mycobacterium tuberculosis (NTM) organisms that may be present in human sputa. Four (4) organisms were tested at high concentration (1 x 10^6 cells/mL of sputa) mixed with *M. bovis* BCG at 2x MTBC LoD. The organisms tested were *M. avium, M. intracellular, M. kansasii and M. malmoense*. MTBC was successfully detected by the BD MAX MDR-TB assay when combined with the simulated high target concentration mixed infection preparations.

Precision

Within-laboratory precision was evaluated for the BD MAX MDR-TB assay at one (1) site. Testing was performed over 12 days, with 2 runs per day (one each by 2 operators), for a total of 24 runs. Each panel contained a wild type *M. tuberculosis* strain (RIF and INH susceptible) and were prepared in an unprocessed sputa matrix. The following concentrations were used as spike levels for the target organism contained in each panel member:

- Resistance Moderate Positive (MP): ≥2 and ≤3x LoD
- MTB Moderate Positive (MP): ≥2 and ≤3x LoD
- Resistance Low Positive (LP): ≥1 and <2x LoD
- MTB Low Positive (LP): ≥1 and <2x LoD
- True negative (TN): Negative sample (no target)

Precision study results for TN, Resistance MP, MTB MP, and Resistance MP samples demonstrated 100% agreement (Table 25). Precision study results for Resistance LP samples demonstrated 98.6% agreement. All the initial non-reportable results, except one, were repeated in accordance with the package insert instructions. Samples that initially gave a <MTB Low POS> result gave the expected result upon repeat.

Table 25: Precision Study Results Using One Lot of the BD MAX MDR-TB Assay

Category	Agreement With Expected Results	
	***M. tuberculosis* (95% CI)**	**Resistance (95% CI)**
MP	100% 72/72 (94.9–100.0)	100% 72/72 (94.9–100.0)
LP	100% 72/72 (94.9–100.0)	98.6% 70/71 (92.4%, 99.8%)
TN[a]	100% 72/72 (94.9–100.0)	100% 72/72 (94.9–100.0)

[a]For the True Negative (TN) category, the reported agreement indicates the percent of negative results.

Reproducibility

The Instrument-to-Instrument reproducibility study was performed using the same panels as described for the Precision study, above.

Samples in each category were tested in triplicate, on five (5) distinct days, by two (2) different technologists, on three (3) different instruments using (one) 1 lot of reagents.

For Instrument-to-Instrument Reproducibility, the overall percent agreement was 100% for MTB MP, MTB LP, Resistance MP, and TN. The overall percent agreement was 97.8% for Resistance LP (Table 26). The quantitative reproducibility across sites and by sample category is presented below in Table 27.

Table 26: Instrument-to-Instrument Reproducibility Study Results Using One Lot of the BD MAX MDR-TB Assay

Category	Instrument 1	Instrument 2	Instrument 3	Overall	
				Agreement	95% CI
TN	100% (30/30)	100% (30/30)	100% (30/30)	100% (90/90)	(95.9–100.0)
MTB LP	100% (30/30)	100% (30/30)	100% (30/30)	100% (90/90)	(95.9–100.0)
Resistance LP	100% (30/30)	96.6% (28/29)	96.7% (29/30)	97.8% (87/89)	(92.2–99.4)
MTB MP	100% (30/30)	100% (30/30)	100% (30/30)	100% (90/90)	(95.9–100.0)
Resistance MP	100% (30/30)	100% (30/30)	100% (30/30)	100% (90/90)	(95.9–100.0)

Table 27: Instrument-to-Instrument Reproducibility Study Underlying Numerical CT Score Overall Results

Variable	Category	Agree/N	Mean	Within Run		Between Run Within Day		Between Day		Between Instrument		Overall	
				SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Ct.Score (MTB1)	MP	59/90	38.6	0.81	2.1	0.00	0.0	0.21	0.6	0.00	0.0	0.84	2.2
	LP	52/90	38.5	0.88	2.3	0.38	1.0	0.00	0.0	0.18	0.5	0.98	2.5
Ct.Score (MTB2)	MP	90/90	35.8	0.70	1.9	0.00	0.0	0.00	0.0	0.12	0.3	0.71	2.0
	LP	90/90	36.1	0.74	2.1	0.00	0.0	0.06	0.2	0.29	0.8	0.80	2.2

NOTE: Values shown are those obtained for the target in the samples that gave an MTB Detected result.

For the Lot-to-Lot reproducibility study, three replicates of samples in each category were tested with three lots of reagents on a single instrument, with two runs per day performed over five distinct days. The panels used were the same as described under the Precision heading, above. Results from 5 days of the Instrument-to-Instrument study were used to comprise data for one lot of reagents for the Lot-to-Lot study. For Lot-to-Lot Reproducibility, the overall percent agreement was 98.9% for MTB MP, MTB LP, and Resistance MP; 96.6% for Resistance LP and 100% for TN, respectively (Table 28).

Table 28: Lot-to-Lot Reproducibility Study Results Using Three Lots of the BD MAX MDR-TB Assay

Category	Lot 1	Lot 2	Lot 3	Overall	
				Agreement	95% CI
TN	100% (30/30)	100% (30/30)	100% (30/30)	100% (90/90)	(95.9%, 100%)
MTB LP	100% (30/30)	100% (30/30)	96.7% (29/30)	98.9% (89/90)	(94.0%, 99.8%)
Resistance LP	96.6% (28/29)	96.7% (29/30)	96.7% (29/30)	96.6% (86/89)	(90.6%, 98.8%)
MTB MP	100% (30/30)	100% (30/30)	96.7% (29/30)	98.9% (89/90)	(94.0%, 99.8%)
Resistance MP	100% (30/30)	96.7% (29/30)	100% (30/30)	98.9% (89/90)	(94.0%, 99.8%)

Carry-Over–Cross-Contamination

A study was conducted to investigate within-run carryover and between-run carryover while processing samples with high bacterial load of MTBC in the BD MAX MDR-TB assay. The positive panel consisted of MTBC organism spiked into STR treated sputum at a concentration of 1 x 10^6 CFU/mL. The negative panel members did not contain any MTBC organism. Twelve (12) replicates of the high positive panel member and 12 replicates of the negative panel member were tested in each run by alternating negative and positive samples. A total of 9 runs containing 24 samples each were run across multiple instruments. Of the 108 negative samples tested in this study, one sample produced a positive result.

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Change History

Revision	Date	Change Summary
(08)	2019-06	Updated R/S for Strain ID TB112 in Table 19. Updated Sputum (CFU/mL) Limit of Detection for *M. tuberculosis* (H37Rv) MTBC in Table 21.
(09)	2020-05	Converted printed instructions for use to electronic format and added access information to obtain the document from bd.com/e-labeling. Intended Use clarified. Additional information added to Reagents and Materials section. Updated Figures 1, 2, and 3. Added limitation regarding pediatric patients. Updated and clarified Performance Characteristics section. Updated Australia and New Zealand Sponsor addresses.
(10)	2020-11	Updated GHS information in Warnings and Precautions. Performance tables were revised following an improvement to RIF resistance detection applied in software. This change resulted in an update to RIF detection numbers in, and related to, tables 2, 3, 5, 8, 9, 15, 16, 19, 25, 26, and 28.

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AAAA-MM-JJ / AAAA-MM (MM = fin du mois)
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GGGG-MM-DD/GGGG-MM (MM = mēneša beigas)
JJJJ-MM-DD / JJJJ-MM (MM = einde maand)
ÅÅÅÅ-MM-DD / ÅÅÅÅ-MM (MM = slutten av måneden)
RRRR-MM-DD / RRRR-MM (MM = koniec miesiąca)
AAAA-MM-DD / AAAA-MM (MM = fim do mês)
AAAA-LL-ZZ / AAAA-LL (LL = sfârşitul lunii)
ГГГГ-ММ-ДД / ГГГГ-ММ (ММ = конец месяца)
RRRR-MM-DD / RRRR-MM (MM = koniec mesiaca)
GGGG-MM-DD / GGGG-MM (MM = kraj meseca)
ÅÅÅÅ-MM-DD / ÅÅÅÅ-MM (MM = slutet av månaden)
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CONTROL +

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Negative control / Отрицателен контрол / Negativní kontrola / Negativ kontrol / Negative Kontrolle / Αρνητικός μάρτυρας / Control negativo / Negatiivne kontroll / Contrôle négatif / Negativna kontrola / Negatív kontroll / Controllo negativo / Неративтік бақылау / 음성 컨트롤 / Neigiama kontrolė / Negatīvā kontrole / Negatieve controle / Kontrola ujemna / Controlo negativo / Control negativ / Отрицательный контроль / Negatif kontrol / Негативний контроль / 阴性对照试剂

STERILE EO

Method of sterilization: ethylene oxide / Метод на стерилизация: етиленов оксид / Způsob sterilizace: etylenoxid / Steriliseringsmetode: ethylenoxid / Sterilisationsmethode: Ethylenoxid / Μέθοδος αποστείρωσης: αιθυλενοξείδιο / Método de esterilización: óxido de etileno / Steriliseerimismeetod: etüleenoksiid / Méthode de stérilisation : oxyde d'éthylène / Metoda sterilizacije: etilen oksid / Sterilizálás módszere: etilén-oxid / Metodo di sterilizzazione: ossido di etilene / Стерилизация әдісі – этилен тотығы / 소독 방법: 에틸렌옥사이드 / Sterilizavimo būdas: etileno oksidas / Sterilizēšanas metode: etilēnoksīds / Gesteriliseerd met behulp van ethyleenoxide / Steriliseringsmetode: etylenoksid / Metoda sterylizacji: tlenek etylu / Método de esterilização: óxido de etileno / Metodă de sterilizare: oxid de etilenă / Метод стерилизации: этиленоксид / Metóda sterilizácie: etylénoxid / Metoda sterilizacije: etilen oksid / Steriliseringsmetod: etenoxid / Sterilizasyon yöntemi: etilen oksit / Метод стерилізації: етиленоксидом / 灭菌方法：环氧乙烷

STERILE R

Method of sterilization: irradiation / Метод на стерилизация: ирадиация / Způsob sterilizace: záření / Steriliseringsmetode: bestråling / Sterilisationsmethode: Bestrahlung / Μέθοδος αποστείρωσης: ακτινοβολία / Método de esterilización: irradiación / Steriliseerimismeetod: kiirgus / Méthode de stérilisation : irradiation / Metoda sterilizacije: zračenje / Sterilizálás módszere: besugárzás / Metodo di sterilizzazione: irradiazione / Стерилизация әдісі – сәуле түсіру / 소독 방법: 방사 / Sterilizavimo būdas: radiacija / Sterilizēšanas metode: apstarošana / Gesteriliseerd met behulp van bestraling / Steriliseringsmetode: bestråling / Metoda sterylizacji: napromienianie / Método de esterilização: irradiação / Metodă de sterilizare: iradiere / Метод стерилизации: облучение / Metóda sterilizácie: ožiarenie / Metoda sterilizacije: ozračavanje / Steriliseringsmetod: strålning / Sterilizasyon yöntemi: irradyasyon / Метод стерилізації: опроміненням / 灭菌方法：辐射

Biological Risks / Биологични рискове / Biologická rizika / Biologisk fare / Biogefährdung / Βιολογικοί κίνδυνοι / Riesgos biológicos / Bioloogilised riskid / Risques biologiques / Biološki rizik / Biológiailag veszélyes / Rischio biologico / Биологиялық тәуекелдер / 생물학적 위험 / Biologinis pavojus / Bioloģiskie riski / Biologisch risico / Biologisk risiko / Zagrożenia biologiczne / Perigo biológico / Riscuri biologice / Биологическая опасность / Biologické riziko / Biološki rizici / Biologisk risk / Biyolojik Riskler / Біологічна небезпека / 生物学风险

Caution, consult accompanying documents / Внимание, направете справка в придружаващите документи / Pozor! Prostudujte si přiloženou dokumentaci! / Forsigtig, se ledsagende dokumenter / Achtung, Begleitdokumente beachten / Προσοχή, συμβουλευτείτε τα συνοδευτικά έγγραφα / Precaución, consultar la documentación adjunta / Ettevaatust! Lugeda kaasnevat dokumentatsiooni / Attention, consulter les documents joints / Upozorenje, koristi prateću dokumentaciju / Figyelem! Olvassa el a mellékelt tájékoztatót / Attenzione: consultare la documentazione allegata / Абайлаңыз, тиісті құжаттармен танысыңыз / 주의, 동봉된 설명서 참조 / Dėmesio, žiūrėkite pridedamus dokumentus / Piesardzība, skatīt pavaddokumentus / Voorzichtig, raadpleeg bijgevoegde documenten / Forsiktig, se vedlagt dokumentasjon / Należy zapoznać się z dołączonymi dokumentami / Cuidado, consulte a documentação fornecida / Atenţie, consultaţi documentele însoţitoare / Внимание: см. прилагаемую документацию / Výstraha, pozri sprievodné dokumenty / Pažnja! Pogledajte priloženа dokumenta / Obs! Se medföljande dokumentation / Dikkat, birlikte verilen belgelere başvurun / Увага: див. супутню документацію / 小心，请参阅附带文档。

Upper limit of temperature / Горен лимит на температурата / Horní hranice teploty / Øvre temperaturgrænse / Temperaturobergrenze / Ανώτερο όριο θερμοκρασίας / Límite superior de temperatura / Ülemine temperatuuripiir / Limite supérieure de température / Gornja dozvoljena temperatura / Felső hőmérsékleti határ / Limite superiore di temperatura / Температураның руқсат етілген жоғарғы шеті / 상한 온도 / Aukščiausia laikymo temperatūra / Augšējā temperatūras robeža / Hoogste temperatuurlimiet / Øvre temperaturgrense / Górna granica temperatury / Limite máximo de temperatura / Limită maximă de temperatură / Верхний предел температуры / Horná hranica teploty / Gornja granica temperature / Övre temperaturgräns / Sıcaklık üst sınırı / Максимальна температура / 温度上限

Keep dry / Пазете сухо / Skladujte v suchém prostředí / Opbevares tørt / Trocklagern / Φυλάξτε το στεγνό / Mantener seco / Hoida kuivas / Conserver au sec / Držati na suhom / Száraz helyen tartandó / Tenere all'asciutto / Құрғақ күйінде ұста / 건조 상태 유지 / Laikykite sausai / Uzglabāt sausu / Droog houden / Holdes tørt / Przechowywać w stanie suchym / Manter seco / A se feri de umezeală / Не допускать попадания влаги / Uchovávajte v suchu / Držite na suvom mestu / Förvaras torrt / Kuru bir şekilde muhafaza edin / Берегти від вологи / 请保持干燥

Collection time / Време на събиране / Čas odběru / Opsamlingstidspunkt / Entnahmeuhrzeit / Ώρα συλλογής / Hora de recogida / Kogumisaeg / Heure de prélèvement / Sati prikupljanja / Mintavétel időpontja / Ora di raccolta / Жинау уақыты / 수집 시간 / Paėmimo laikas / Savākšanas laiks / Verzameltijd / Tid prøvetaking / Godzina pobrania / Hora de colheita / Ora colectării / Время сбора / Doba odberu / Vreme prikupljanja / Uppsamlingstid / Toplama zamanı / Час забору / 采集时间

Peel / Обелете / Otevřete zde / Åbn / Abziehen / Αποκολλήστε / Desprender / Koorida / Décoller / Otvoriti skini / Húzza le / Staccare / Ұстіңгі қабатын алып таста / 벗기기 / Plėšti čia / Atīrmēt / Schillen / Trekk av / Oderwać / Destacar / Se dezlipeşte / Отклеить / Odtrhnite / Oljuštiti / Dra isär / Ayırma / Відклеїти / 撕下

Perforation / Перфорация / Perforace / Perforering / Διάτρηση / Perforación / Perforatsioon / Perforacija / Perforálás / Perforazione / Тесік тесу / 절취선 / Perforacija / Perforācija / Perforatie / Perforacja / Perfuração / Perforare / Перфорация / Perforácia / Perforasyon / Перфорація / 穿孔

Do not use if package damaged / Не използвайте, ако опаковката е повредена / Nepoužívejte, je-li obal poškozený / Må ikke anvendes hvis emballagen er beskadiget / Inhal beschädigter Packungnicht verwenden / Μη χρησιμοποιείτε εάν η συσκευασία έχει υποστεί ζημιά. / No usar si el paquete está dañado / Mitte kasutada, kui pakend on kahjustatud / Ne pas l'utiliser si l'emballage est endommagé / Ne koristiti ako je oštećeno pakiranje / Ne használja, ha a csomagolás sérült / Non usare se la confezione è danneggiata / Егер пакет бұзылған болса, пайдаланба / 패키지가 손상된 경우 사용 금지 / Jei pakuotė pažeista, nenaudoti / Nelietot, ja iepakojums bojāts / Niet gebruiken indien de verpakking beschadigd is / Må ikke brukes hvis pakke er skadet / Nie używać, jeśli opakowanie jest uszkodzone / Não usar se a embalagem estiver danificada / A nu se folosi dacă pachetul este deteriorat / Не использовать при повреждении упаковки / Nepoužívajte, ak je obal poškodený / Ne koristite ako je pakovanje oštećeno / Använd ej om förpackningen är skadad / Ambalaj hasar görmüşse kullanmayın / Не використовувати за пошкодженої упаковки / 如果包装破损，请勿使用

Keep away from heat / Пазете от топлина / Nevystavujte přílišnému teplu / Må ikke udsættes for varme / Vor Wärme schützen / Κρατήστε το μακριά από τη θερμότητα / Mantener alejado de fuentes de calor / Hoida eemal valgusest / Protéger de la chaleur / Držati dalje od izvora topline / Óvja a melegtől / Tenere lontano dal calore / Салқын жерде сақта / 열을 피해야 함 / Laikyti atokiau nuo šilumos šaltinių / Sargāt no karstuma / Beschermen tegen warmte / Må ikke utsettes for varme / Przechowywać z dala od źródeł ciepła / Manter ao abrigo do calor / A se feri de căldură / Не нагревать / Uchovávajte mimo zdroja tepla / Držite dalje od toplote / Får ej utsättas för värme / Isıdan uzak tutun / Берегти від дії тепла / 请远离热源

Cut / Срежете / Odstřihněte / Klip / Schneiden / Κόψτε / Cortar / Lõigata / Découper / Reži / Vágja ki / Tagliare / Кесіңіз / 잘라내기 / Kirpti / Nogriezt / Knippen / Kutt / Odciąć / Cortar / Decupaţi / Отрезать / Odstrihnite / Iseći / Klipp / Kesme / Розрізати / 剪下

Collection date / Дата на събиране / Datum odběru / Opsamlingsdato / Entnahmedatum / Ημερομηνία συλλογής / Fecha de recogida / Kogumiskuupäev / Date de prélèvement / Dani prikupljanja / Mintavétel dátuma / Data di raccolta / Жинаған тізбекүні / 수집 날짜 / Paėmimo data / Savākšanas datums / Verzameldatum / Dato prøvetaking / Data pobrania / Data de colheita / Data colectării / Дата сбора / Dátum odberu / Datum prikupljanja / Uppsamlingsdatum / Toplama tarihi / Дата забору / 采集日期

µL/test / µL/тест / µL/Test / µL/εξέταση / µL/prueba / µL/teszt / µL/테스트 / мкл/тест / µL/tyrimas / µL/pārbaude / µL/teste / мкл/аналіз / µL/检测

Keep away from light / Пазете от светлина / Nevystavujte světlu / Må ikke udsættes for lys / Vor Licht schützen / Κρατήστε το μακριά από το φως / Mantener alejado de la luz / Hoida eemal valgusest / Conserver à l'abri de la lumière / Držati dalje od svjetla / Fény nem érheti / Tenere al riparo dalla luce / Қараңғыланған жерде ұста / 빛을 피해야 함 / Laikyti atokiau nuo šilumos šaltinių / Sargāt no gaismas / Niet blootstellen aan zonlicht / Må ikke utsettes for lys / Przechowywać z dala od źródeł światła / Manter ao abrigo da luz / Feriţi de lumină / Хранить в темноте / Uchovávajte mimo dosahu svetla / Držite dalje od svetlosti / Får ej utsättas för ljus / Işıktan uzak tutun / Берегти від дії світла / 请远离光线

Hydrogen gas generated / Образуван е водород газ / Možnost úniku plynného vodíku / Frembringer hydrogengas / Wasserstoffgas erzeugt / Δημιουργία αερίου υδρογόνου / Producción de gas de hidrógeno / Vesinikgaasi tekitatud / Produit de l'hydrogène gazeux / Sadrži hydrogen vodik / Hidrogén gázt fejleszt / Produzione di gas idrogeno / Газтектес сутеги пайда болды / 수소 가스 생성됨 / Išskiria vandenilio dujas / Rodas ūdeņradis / Waterstofgas gegenereerd / Hydrogengass generert / Powoduje powstawanie wodoru / Produção de gás de hidrogénio / Generare gaz de hidrogen / Выделение водорода / Vyrobené použitím vodíka / Oslobađa se vodonik / Genererad vätgas / Açığa çıkan hidrojen gazı / Реакція з виділенням водню / 会产生氢气

Patient ID number / ИД номер на пациента / ID pacienta / Patientens ID-nummer / Patienten-ID / Αριθμός αναγνώρισης ασθενούς / Número de ID del paciente / Patsiendi ID / No d'identification du patient / Identifikacijski broj pacijenta / Beteg azonosító száma / Numero ID paziente / Пациенттің идентификациялық нөмірі / 환자 ID 번호 / Paciento identifikavimo numeris / Pacienta ID numurs / Identificatienummer van de patiënt / Pasientens ID-nummer / Numer ID pacjenta / Número da ID do doente / Număr ID pacient / Идентификационный номер пациента / Identifikačné číslo pacienta / ID broj pacijenta / Patientnummer / Hasta kimlik numarası / Ідентифікатор пацієнта / 患者标识号

Fragile, Handle with Care / Чупливо, Работете с необходимото внимание. / Křehké. Při manipulaci postupujte opatrně. / Forsigtig, kan gå i stykker. / Zerbrechlich, vorsichtig handhaben. / Εύθραυστο. Χειριστείτε το με προσοχή. / Frágil. Manipular con cuidado. / Õrn, käsitsege ettevaatlikult. / Fragile. Manipuler avec précaution. / Lomljivo, rukujte pažljivo. / Törékeny! Óvatosan kezelendő. / Fragile, maneggiare con cura. / Сынғыш, абайлап пайдаланыңыз. / 조심 깨지기 쉬운 처리 / Trapu, elkitės atsargiai. / Trausls; rīkoties uzmanīgi / Breekbaar, voorzichtig behandelen. / Ømtålig, håndter forsiktig. / Krucha zawartość, przenosić ostrożnie. / Frágil, Manuseie com Cuidado. / Fragil, manipulaţi cu atenţie. / Хрупкое! Обращаться с осторожностью. / Krehké, vyžaduje sa opatrná manipulácia. / Lomljivo - rukujte pažljivo. / Bräckligt. Hantera försiktigt. / Kolay Kırılır, Dikkatli Taşıyın. / Тендітна, звертатися з обережністю / 易碎，小心轻放

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