A Multi-Laboratory, Multi-Country Study to Determine Bedaquiline MIC Quality Control Ranges for Phenotypic Drug-Susceptibility Testing

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Abstract

Objectives: The aim of this study was to establish standardized drug susceptibility testing (DST) methodologies and reference minimal inhibitory concentration (MIC) quality control (QC) ranges for bedaquiline, a diarylquinoline antimycobacterial, used in the treatment of adults with multidrug-resistant tuberculosis.

Methods: Two tier-2 QC reproducibility studies of bedaquiline DST were conducted in eight laboratories using Clinical Laboratory and Standards Institute (CLSI) guidelines. Agar dilution and broth microdilution methods were evaluated. *Mycobacterium tuberculosis* H37Rv was used as the QC reference strain. Bedaquiline MIC frequency, mode, and geometric mean were calculated. When resulting data occurred outside predefined CLSI criteria, the entire laboratory dataset was excluded.

Results: For the agar dilution MIC, a 4-dilution QC range (0.015–0.12 µg/ml) centered around the geometric mean included 95.8% (7H10 agar dilution; 204/213 observations with one dataset excluded) or 95.9% (7H11 agar dilution; 232/242) of bedaquiline MICs. For the 7H9 broth microdilution MIC, a 3-dilution QC range (0.015–0.06 µg/ml) centered around the mode included 98.1% (207/211 with one dataset excluded) of bedaquiline MICs. Microbiological equivalence was demonstrated for bedaquiline MICs determined using 7H10 agar and 7H11 agar, but not for bedaquiline MICs determined using 7H9 broth and 7H10 agar or 7H9 broth and 7H11 agar.

Conclusions: Bedaquiline DST methodologies and MIC QC ranges against H37Rv *M. tuberculosis* reference strain have been established: 0.015–0.12 µg/ml for 7H10 and 7H11 agar dilution MICs, and 0.015–0.06 µg/ml for the 7H9 broth microdilution MIC. These methodologies and QC ranges will be submitted to CLSI and EUCAST to inform future research and provide guidance for routine clinical bedaquiline DST in laboratories worldwide.

Introduction

Newer drugs are being developed to counter the growing problem of multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis* (MTB). Of the 9.6 million estimated new MTB cases occurring globally in 2014, 3.3% were MDR, added to 20% of previously treated TB cases estimated to have MDR; this equates to an overall estimate of 480 000 people with MDR-TB annually. Furthermore, current treatment outcome data for patients started on MDR-TB treatment in 2015 suggest a success rate of only 50% (1). The approval of new antimycobacterials effective against MDR-TB strains has highlighted the need for validated and standardized drug susceptibility testing (DST) methods to enhance patient care and for facilitating drug-resistance surveillance.

Bedaquiline, a diarylquinoline antimycobacterial (2), has received accelerated/conditional approval for use based on Phase II trials, in the US (2012), the EU (2014) and 7 high MDR-TB burden countries (3–8). Interim policy guidance for the use of bedaquiline as part of combination therapy for adults who have pulmonary MDR-TB has been issued by the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC) (9,10).

Preliminary DST methodology for bedaquiline was previously piloted and then used in the two Phase II clinical studies (3–6). In these studies, bedaquiline DST was performed by 7H11 agar dilution and 7H9 broth microdilution methods using the resazurin microtiter assay (REMA) (11,12). For bedaquiline DST, the standard quality control (QC) strain MTB H37Rv should be used under the same conditions as the clinical MTB isolates to ensure that the bedaquiline minimal inhibitory concentration (MIC) of the reference falls within a predefined QC range. For QC purposes when testing clinical isolates prior to the present study, the provisional bedaquiline MIC ranges against strain H37Rv were 0.03–0.12 µg/ml for 7H11 agar and 0.03–0.12 µg/ml for REMA (7H9 broth) (7). These provisional DST methodologies and MIC QC ranges for bedaquiline required validation in a multi-laboratory study. The validation of bedaquiline phenotypic DST methods is particularly important since it is not foreseeable that a rapid

bedaquiline molecular or genotypic DST method will be available in the near future for the following reasons: 1) mutations in the bedaquiline target *atpE* gene that lead to high bedaquiline MICs have only been observed *in vitro* so far and not in MTB isolates from MDR-TB patients. 2) Mutations in *Rv0678*, a transcriptional repressor of the genes encoding the MmpS5-MmpL5 efflux pump, lead to 2-8 fold MIC increases and low level resistance to and have been observed in isolates obtained both *in vitro* and in the clinic (13,14). These mutations include single nucleotide insertions, deletions and substitutions, and large deletions and random insertions of insertion sequence elements. 3) Mutations in *pepQ* (*Rv2435c)*, a putative Xaa-Pro aminopeptidase, produce modest increase (up to 4-fold) in bedaquiline and clofazimine MICs but significantly reduce the efficacy of bedaquiline and clofazimine in the mouse model (15). Similar to *atpE*, the mutations in *Rv0678* and *pepQ* are spread over the length of the gene. Additional resistance associated variants (RAVs) carry mutations in the intergenic region between *Rv0678* and *Rv0677c* (16). Thus, *Rv0678*-, *pepQ*- and *atpE*-based rapid genotypic DST is not feasible using the current single nucleotide polymorphism (SNP) molecular DST platform. A limited number of *atpE* mutations have been examined. 4) As with most chromosome-borne antimicrobial resistance genetic tests, there is lack of an algorithm to translate any known mutations in either *atpE, Rv0678* or *pepQ* into bedaquiline MICs. Because of these shortcomings, reliable bedaquiline phenotypic DST methods are necessary.

Two multi-laboratory studies were conducted to establish and validate standard DST methodologies for bedaquiline, as well as determine reference bedaquiline MIC QC ranges on solid and liquid medium. The validation methods were adapted from Clinical Laboratory and Standards Institute (CLSI) documents M07-A9 (17) and M24-A2 (18), and criteria for establishing DST QC ranges for new antimicrobial agents were sourced from CLSI Document M23-A3 (19).

Materials and methods

Study design

Two concurrent multi-laboratory, multi-country reproducibility studies were performed using bedaquiline phenotypic DST: one study was conducted using 7H10 and 7H11 agar dilution MIC (Study TMC207-PMR-1988-003), and another study was performed using 7H9 broth microdilution MIC (Study TMC207-PMR-1988-004). Both studies conformed to CLSI tier-2 criteria, as they sought to establish acceptable QC ranges for bedaquiline.

Eight independent laboratories participated (a minimum of seven laboratories is required under CLSI tier-2 criteria), with each laboratory was instructed to perform 10 replicate tests on separate days using three separate media lots from different manufacturers and an internationally recognized MTB reference strain according to CLSI Document M23-A3 (19). The study protocol was developed by consensus among participating investigators. None of the laboratories had access to the results of the others.

Studies were performed according to CLSI Document M07-A9 (17) with respect to preparation of the drug stock concentration, dilution process for the 7H10 and 7H11 agar, and based on the classical method for DST as outlined in M24-A2 (18) for the QC reference strain and the preparation of the inoculum.

The two studies evaluated the reproducibility of the DST methods within each participating laboratory, between laboratories and between reagent lots. The MICs obtained from agar DST method were also compared with those from broth method.

Participating laboratories

The eight participating laboratories were geographically diverse being situated on three different continents. The investigators and their laboratories included CLSI members or advisors, the WHO Supranational Reference Laboratory Network (SRLN), the US CDC and other internationally recognized TB laboratories.

Materials

Isolates

The reference strain used was MTB H37Rv, which was originally obtained from the American Type Culture Collection (ATCC number 27294). Each laboratory used its own stock of this H37Rv reference strain.

Antimicrobials

Bedaquiline was provided to each laboratory by the manufacturer (Janssen Infectious Diseases BVBA, Beerse, Belgium).

Labware

All regular plates and microtiter plates used to perform the DST were polystyrene, as polypropylene can lead to errors in MIC determination for bedaquiline (20).

Culture media

For the agar dilution study, each laboratory was provided with three separate lots of Middlebrook 7H10 agar and three separate lots of Middlebrook 7H11 agar in powder form. Media were obtained from three different manufacturers: Becton Dickinson (Franklin Lakes, New Jersey; lot number 3116410 for 7H10 agar and 3189213 for 7H11 agar); Sigma-Aldrich (St Louis, Missouri; lot numbers BCBL7582V and BCBL4307V, respectively); and Titan Biotech Ltd (Delhi, India; lot numbers M2B4KN01 and M7I6KN01, respectively). For the purpose of the analyses, each type of agar (7H10 or 7H11) was assigned a number from 1 to 3 depending on the manufacturer. Middlebrook oleic acid albumin dextrose catalase (OADC) growth supplement was also provided (Becton Dickinson, Franklin Lakes, New Jersey).

For the broth microdilution study, Middlebrook 7H9 broth base and OADC were obtained from Becton Dickinson (Franklin Lakes, New Jersey). Each laboratory was provided with three separate lots of custom-made frozen 96-well polystyrene microtiter plates (Thermo Fisher Scientific Inc, Waltham, Massachusetts; lot numbers 14181, 14202 and 14203). Laboratories

were also provided with 12.5 ml sterile deionized water tubes and saline Tween broth to reconstitute the mycobacterial inoculum.

Löwenstein-Jensen medium is not recommended for bedaquiline DST due to its high protein content and was therefore not evaluated in this study (7,20).

MIC determination by the agar dilution method

Preparation of agar media

The 7H10 or 7H11 agar media were prepared by the investigator according to CLSI Document M07-A9 (17).

Preparation of bedaquiline dilutions

Bedaquiline was dissolved in dimethylsulfoxide (DMSO) to give a 200 µg/ml solution, and then 2-fold serial dilutions were further made from 200 µg/ml down to 0.8 µg/ml in DMSO (working solutions). Storage of aliquots of these solutions in DMSO was allowed for up to 3 months at -20°C, but once thawed, the solutions could not be stored further or refrozen. The working solutions in DMSO were diluted 1/100 in 7H10 or 7H11 agar medium to obtain the final desired concentrations of 2, 1, 0.5, 0.25, 0.12, 0.06, 0.03, 0.015 and 0.008 µg/ml in the polystyrene plates to be used for the DST.

MTB culture and preparation of suspension

An MTB H37Rv suspension was prepared in BSL3 laboratories according to the procedures in use for MTB. MTB isolates were grown on 7H11/7H10 media (or Lowenstein-Jensen medium). Several loops, 2–5 mg of mycobacterial growth were harvested, with the aim of selecting MTB from each colony. Cultures older than 21 days were not considered acceptable as they may yield unreliable DST results. The colonies were transferred to a 16 $\times$ 125 mm screw cap tube containing 5 ml sterile saline Tween and 6–8 glass beads. The suspension was homogenized with a test tube mixer for 5–10 min and larger particles allowed to settle for 10 min. The supernatant suspension was then harvested and the density adjusted to that of a McFarland standard 1 suspension (~5 $\times$ 10^7 colony forming units [CFU]/ml) using sterile deionized water or

saline (18,21). There is good concordance between the McFarland Scale and CFU/ml for MTB (22). A new inoculum was prepared each time a set of agar plates was inoculated.

Inoculation of culture media

Inoculum in all experiments was standardized: Working suspensions were made using a 10-fold dilution of the MTB H37Rv suspension with sterile deionized water or saline. The undiluted (10^0) MTB suspension, containing ~5×10^7 CFU/ml, was mixed, and 0.1 ml was transferred to 0.9 ml of the first dilution tube (10^{-1}) (~5×10^6 CFU/ml). Care was taken to ensure all inocula were of the same standard size and fell within 0.5 log of the target in order for the resulting MIC values to be accepted as valid.

The pre-prepared bedaquiline-containing 7H10 or 7H11 agar plates were then inoculated with 0.1 ml of the 10^{-1} dilution, resulting in 5×10^5 CFU/ml plated.

To ascertain the accuracy of the inoculum plated, additional 10-fold serial dilutions of the suspension (10^{-3}, 10^{-4} and 10^{-5}) were made from the 10^{-1} dilution tube. The 7H10 or 7H11 polystyrene plates containing no drugs were then inoculated with 0.1 ml of the 10^{-3}, 10^{-4} and 10^{-5} dilutions, resulting in plates containing 5 000 CFU, 500 CFU and 50 CFU, respectively. These plates also served as positive control for growth.

Incubation

Inoculated polystyrene plates were incubated the right way up for 1–2 days at 35–37ºC until the inoculum was dry; they were then turned upside down. For incubators that were not humidified, plates were kept in plastic bags.

MIC assessment

Results were reported at 21 days post-inoculation. The MIC was defined as the lowest drug concentration (in µg/ml) that resulted in complete (100%) inhibition of visual growth (17). The positive control was checked to ensure that it showed mycobacterial growth.

MIC determination by broth microdilution method

Custom-made frozen microtiter plates for 'Research Use Only' were used and were pre-prepared with bedaquiline serial dilutions in 2X supplemented 7H9 media (7H9-S: 7H9 broth/10% OADC, Becton Dickinson) at 2X final drug concentrations.

MTB culture and preparation of suspension

MTB isolates were grown on 7H11 agar medium (or Lowenstein-Jensen) and colonies resuspended in 7H9-S. The turbidity of the MTB H37Rv suspension was adjusted with phosphate-buffered saline to match that of a McFarland standard 1 suspension, corresponding to ~5×10^7 CFU/ml.

Inoculation of the microtiter plates

A 2X inoculum of MTB H37Rv was prepared by adding (with a calibrated micro-pipetting device) 300 µl of the McFarland standard 1 suspension to 14.7 ml of sterile deionized water (50-fold dilution) in a polystyrene tube to give 1×10^6 CFU/ml. The 2X inoculum was poured into a disposable inoculum reservoir and then 100 µl transferred to the microtiter plate wells, using an 8 or 12 channel micro-pipette and sterile tips with filters. Inoculum was added to all wells (including the growth control wells) except the negative control wells which received 100 µl of sterile deionized water. The final inoculum size in the plates was 5×10^5 CFU/ml and the final bedaquiline concentrations were 4, 2, 1, 0.5, 0.25, 0.12, 0.06, 0.03, 0.015, 0.008 and 0 µg/ml.

Incubation

After inoculation, the microtiter plates were sealed in plastic bags (10 plates per bag) and incubated at 35–37ºC.

MIC assessment

Results were reported at days 7, 10 and 14 post-inoculation, with the microtiter plates read according to the usual laboratory procedure. The growth control was checked to ensure that it showed mycobacterial growth and the negative control to ensure it showed no growth. Any

negative control well with a turbid appearance was suspected of contamination and results discounted as invalid.

Data collection and statistical methods

To ensure consistent data capture and reporting, and to allow compilation of the final analyses, investigators were pre-supplied with data collection forms. Each laboratory was assigned a unique identification number based on the order in which data were submitted. QC checks were performed on the datasets from all laboratories, and inconsistent data queried with the investigator who was then required to resubmit an updated file for the final analyses. Examples of inconsistencies included MIC values not within the specified dilution range, commas used as decimal separator, and erroneous dilutions. All finalized MIC data were consolidated in a master file and a final QC check performed.

Statistical analysis of MIC distribution frequencies, the modes (most frequently occurring MIC value) and the geometric mean MICs were performed using SAS software version 9.2 (SAS Institute). For MIC values preceded by '<', the sign was ignored, and the lower end MIC value of the range was reported as '≤'. For MIC values preceded by '>', the MIC value was reported as '≥' the next dilution (e.g.' >1' was reported as '≥2').

CLSI Document M23-A3 (19) instructs that whenever possible, the low end of the QC range for dilution testing should include concentrations that can be ‘accurately’ prepared. In addition, dilutions should extend to no more than five dilutions below a drug’s susceptibility breakpoint. For bedaquiline, the provisional EUCAST susceptibility breakpoint (S ≤0.25 µg/ml) (23) was used as a reference to select the lowest dilution. Initial QC ranges were determined by centering on the MIC mode ±1 dilution and doubling dilution over a 3-dilution QC range (19). When the mode occurred at the end of the proposed dilution range, the geometric mean was used instead. The proposed QC range was required to encompass at least 95% of the observed MIC values. In the event that a QC range over 3-dilutions could not be established, a 4-dilution QC range was analyzed. In this case, the initial proposed range was adjusted: 1) to include at

least 95% of the observed MIC values to accommodate variability expected in routine testing; 2) if a 'shoulder' off the modal value with ≥60% data points of the mode was observed; 3) when a bimodal distribution was observed. If none of these criteria was met, it was concluded that the QC range could not be established. Following these initial analyses, if a laboratory produced outlying data, their entire dataset (for all three media lots) was discarded, and the analyses repeated with the remaining laboratories. Similarly, if a medium lot produced outlying data, the lot from all laboratories would be excluded from the analyses (19). In addition, one laboratory performed 12 replicate tests for each lot and another performed 11 tests. Therefore, the number of observations did not always add up to the preplanned value of 240 (e.g. 8 laboratories $\times$ 30 tests).

A final analysis was performed to determine any potential correlations between the different DST media: 7H10 agar versus 7H11 agar; 7H10 agar versus 7H9 broth; 7H11 agar versus 7H9 broth. Firstly, the Pearson correlation coefficient (R-values) and p-values were calculated using regression analysis on a $\log_2$ scale. Secondly, a microbiologically meaningful inter-method correlation was performed to establish whether the two media were comparable (19). Correlation was assessed at ±1 $\log_2$ dilution step and included ≥100 data points from each of the two media being compared. To be considered microbiologically significant, the target correlation between the two media was defined as ≥90% essential agreement (19).

Results

Establishment of bedaquiline MIC QC ranges

7H10 agar dilution MIC

In an initial analysis of data from all laboratories, comprising 243 observations (Table S1), the mode MIC for bedaquiline was 0.03 µg/ml and the geometric mean was 0.041 µg/ml. A 3-dilution QC range centered around the mode was found to contain only 81.9% (199/243) of the observed bedaquiline MIC values. Moreover, a 4-dilution QC range covering 0.015–0.12 µg/ml

and centered either around the mode or the geometric mean was found to contain only 90.9% (221/243) of bedaquiline MIC values (Data not shown). However, the bedaquiline MIC was found to be unusually high, at 0.25 µg/ml, for one laboratory (Lab-5) for 7H10 agar Lot-1. In line with the protocol (19), all bedaquiline DST data from Lab-5 for all three lots of media were therefore excluded from the bedaquiline MIC QC range assessment for the 7H10 agar dilution method.

Following the exclusion of the Lab-5 data, a revised mode and geometric mean for bedaquiline MIC was calculated based on a total of 213 observations. The resulting values were 0.06 µg/ml and 0.041 µg/ml, respectively. Repeating the 4-dilution QC range (0.015–0.12 µg/ml) centered around the geometric mean resulted in 95.8% (204/213) of the bedaquiline MIC values being included. The required CLSI criteria were, therefore, met (19) and the bedaquiline MIC QC range for the 7H10 agar dilution method was set at 0.015–0.12 µg/ml (Figure 1a).

The source of 7H10 agar media did not appear to affect bedaquiline MIC determination, and a unimodal bedaquiline MIC distribution pattern was observed for each lot. The three different media lots made similar contributions to the overall bedaquiline MIC distribution, with the exception of Lot-3, which showed a high proportion of bedaquiline MICs at 0.015 µg/ml compared with the other lots (Figure 2a).

7H11 agar dilution MIC

In the initial analysis of data from all laboratories (242 observations) (Table S2), the mode MIC for bedaquiline was 0.06 µg/ml and the geometric mean was 0.043 µg/ml. A 3-dilution QC range centered around the mode was found to contain only 90.9% (220/242) of the observed bedaquiline MIC values. However, a 4-dilution QC range covering 0.015–0.12 µg/ml and centered either around the mode or the geometric mean was found to contain of 95.9% (232/242) of the bedaquiline MIC values. Since the CLSI criteria were met (19), the bedaquiline MIC QC range for the 7H11 agar dilution method was set at 0.015–0.12 µg/ml (Figure 1b). The source of 7H11 agar media did not appear to affect bedaquiline MIC determination, with all

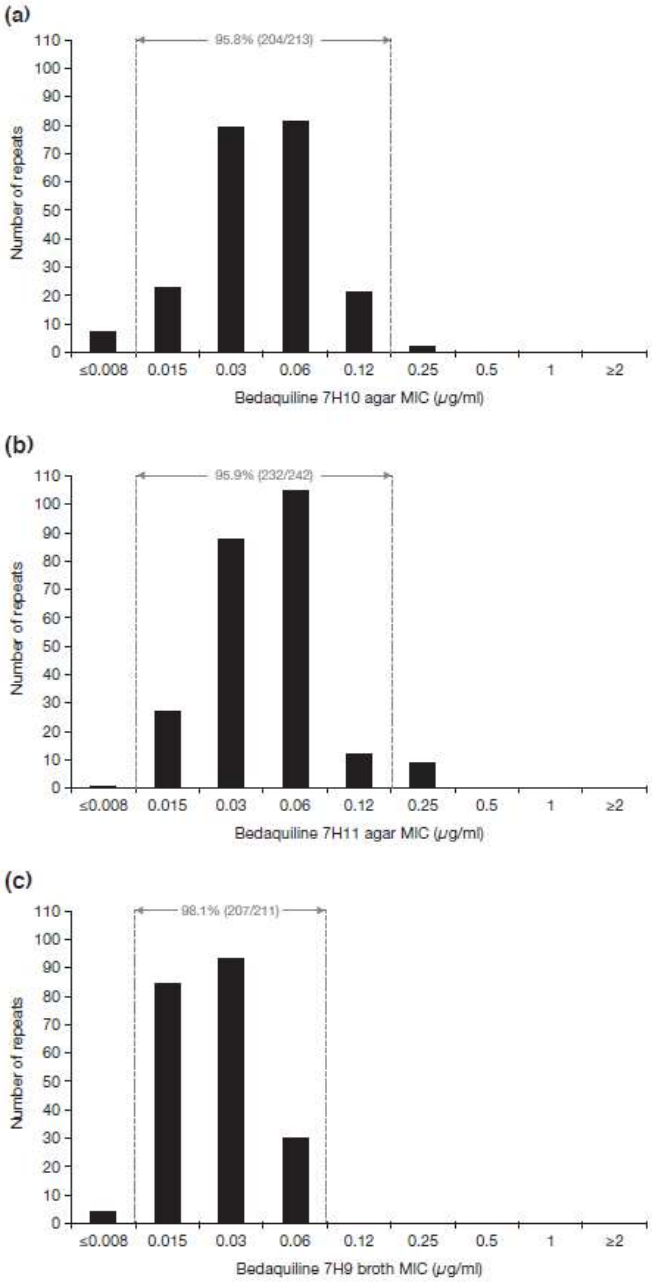

Figure 1. Bedaquiline MIC distributions against MTB H37Rv and QC ranges (a) 7H10 agar including data using all media lots but excluding data from Lab-5; (b) 7H11 agar including data from all laboratories and using all media lots; (c) 7H9 broth using all custom-made microtiter plates lots and excluding Lab-1 data.

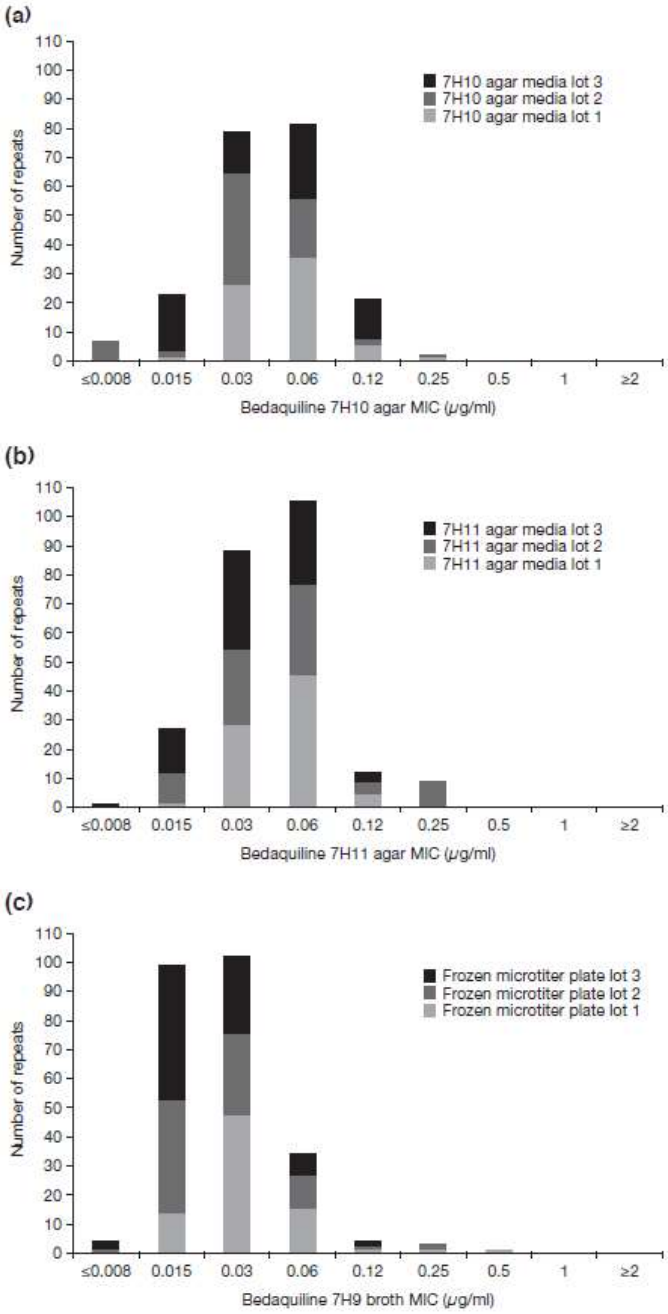

Figure 2. Bedaquiline MIC distributions against MTB H37Rv according to media lot (a) and (b) or (c) 96-well microtiter plate lot: (a) 7H10 agar excluding data from Lab-5; (b) 7H11 agar including data from all laboratories and using all media lots; (c) 7H9 broth including data from all laboratories and using all microtiter plate lots.

three lots contributing equally to the overall bedaquiline MIC distribution, and a unimodal bedaquiline MIC distribution pattern was observed for each lot (Figure 2b).

7H9 broth microdilution MIC

In the initial analysis of the 7H9 broth microdilution method comprising a total of 247 observations (Table S3), the bedaquiline MIC mode was calculated as 0.03 µg/ml and the geometric mean was 0.027 µg/ml. A 3-dilution QC range centered around the mode was found to include 95.1% (235/247) of the bedaquiline MIC values.

Overall, there were few unexpected MICs values between laboratories and between microtiter plate lots. Lab-1 reported 3 observations of bedaquiline MIC values of 0.25 µg/ml, of which 2 instances occurred in Lot-1 and 1 occurred in Lot-2 (Text S1). The same laboratory also had 1 observation of bedaquiline MIC value of 0.5 µg/ml in Lot-1. High MICs represented 11% (4/36) of the data generated by Lab-1. Such high MICs had not been seen previously for bedaquiline against a pan-susceptible strain and disagreed with the results of the other study sites. Therefore, all bedaquiline MIC data from Lab-1 were excluded from the analyses according to the protocol (19).

Following the exclusion of the Lab-1 data, the new analysis, based on a total of 211 observations, showed a mode of 0.03 µg/ml and a geometric mean of 0.025 µg/ml. A 3-dilution QC range based on the mode ±1 dilution included 98.1% (207/211) of the total observations (Figure 1c). A shoulder at 0.015 µg/ml with more than 60% of the mode was noticeable. However, the lower bound of the QC range was not extended to a 4-dilution range as this would have included a concentration that cannot be accurately measured, consistent with the CLSI Document M23(19).

Therefore, the bedaquiline MIC QC range for the 7H9 broth microdilution method was set at 0.015–0.06 µg/ml (Figure 1c). Analysis of MIC values including Lab-1 by manufactured lots of 96-well microtiter plates showed a balanced contribution of each lot to the bedaquiline MIC distribution (Figure 2c).

Final bedaquiline MIC QC ranges for phenotypic DST

Based on the overall data, bedaquiline MIC QC ranges against the MTB reference strain H37Rv have been defined (Table 1). For all three media, the lower limit of the MIC QC range was 0.015 µg/ml; the upper limit was 0.12 µg/ml for 7H10 and 7H11 agar, and 0.06 µg/ml for 7H9 broth.

Table 1. Bedaquiline MIC QC ranges against *Mycobacterium tuberculosis* H37Rv

Bedaquiline Minimal Inhibitory Concentration (µg/ml)		
7H9 broth	**7H10 agar**	**7H11 agar**
0.015–0.06	0.015–0.12	0.015–0.12

Comparison of bedaquiline MICs in different media

For the correlation between 7H10 versus 7H11 agar, all data from Lab-5 were excluded. Similarly, all data from Lab-5 and Lab-1 were excluded in the correlations of 7H9 broth versus 7H10 agar and 7H9 broth and 7H11 agar, as per protocol.

Comparison of 7H10 and 7H11 agar dilution MICs

Regression analysis revealed a statistically significant correlation between bedaquiline MICs obtained with 7H10 agar and 7H11 agar dilution (*n*=212; Pearson Correlation Coefficient: 0.58550; *P*≤0.0001), (Fig. S1a). The microbiologically meaningful inter-method correlation (with ±1 dilution) established that the 7H10 and 7H11 agar media were comparable as there was 93.9% (199/212) essential agreement between the two.

Comparison of 7H10 agar dilution and 7H9 broth microdilution MICs

The Pearson correlation coefficient was –0.15700 (n=178) (Fig. S1b). There was no statistically significant correlation for BDQ MICs determined for 7H9 broth and 7H10 agar media. Furthermore, only 72.5% essential agreement between the two media was demonstrated, which is lower than the 90% target value used to define microbiologic equivalence (19). Therefore,

when performing DST of bedaquiline, the 7H10 agar dilution and 7H9 broth microdilution MICs were deemed not equivalent.

Comparison of 7H11 agar dilution and 7H9 broth microdilution MICs

Similar results were obtained when comparing the 7H11 agar dilution and 7H9 broth microdilution MICs. The Pearson correlation coefficient was –0.22055 (*n*=177) (Fig. S1c). There was no statistically significant correlation for BDQ MICs determined for 7H9 broth and 7H11 agar media. Only 74.6% essential agreement was demonstrated between the two media. The 7H11 agar dilution and 7H9 broth microdilution MICs were deemed not equivalent for performing DST of bedaquiline.

Discussion

These two concurrent, multi-country, tier-2 QC studies analyzed a total of 666 DST results (213 observations for the 7H10 agar dilution, 242 for the 7H11 agar dilution and 211 for the 7H9 broth microdilution methods) generated by eight separate laboratories. Based on the overall data, bedaquiline MIC QC ranges for MTB H37Rv reference strain were established, and DST methodology was standardized for 7H10 and 7H11 agar dilution and 7H9 broth microdilution MIC. The two agar media were shown to be microbiologically equivalent but bedaquiline DST using 7H9 broth microdilution MIC was not equivalent to the agar dilution MIC.

Strengths of the studies included the design, which adhered to strict CLSI criteria (19). The study protocols were developed by adapting the CLSI reference standard for DST methods for aerobic bacteria (17) and Mycobacteria, Nocardiae, and other aerobic Actinomycetes (18). This adaptation was performed using feedback from the investigators and thus the study findings have been produced through a consensus methodology. The robustness of the findings may have been aided by the participating laboratories being highly experienced in MTB DST, with the investigators being members of CLSI, US CDC and internationally recognized

tuberculosis laboratories, such as members of the WHO SRLN. The considerable geographical diversity across the eight laboratories demonstrates that the findings were reproduced globally.

Phenotypic DST using agar-based methods is considered to be generally reliable for drugs such as isoniazid, rifampicin and, to a lesser extent, kanamycin but can be variable for others such as ofloxacin, ethionamide and para-aminosalicylic acid (24). Most clinical microbiology laboratories do not yet have experience in performing phenotypic DST with bedaquiline as this anti-mycobacterial drug has only recently been approved. Documentation of the methodologies for bedaquiline phenotypic DST is therefore important. 7H11 agar was originally developed to facilitate the growth of fastidious MTB isolates, particularly MDR and extensively drug resistant strains, and only differs from 7H10 in that it contains a pancreatic digest of casein. However, some researchers have suggested that the supplementation with casein pancreatic digest makes no difference to the growth of MTB. Moreover, studies evaluating different media for MTB detection in clinical samples have produced contradictory results regarding whether 7H10 or 7H11 agar media is more reliable (25,26). Hence, there is no consensus among laboratories for preference between these two agar media for growth of MTB, with use largely dictated by historical preference.

On the basis of the observed results, bedaquiline phenotypic DST can be performed on 7H10 and 7H11 agar interchangeably. However, no equivalence was demonstrated for bedaquiline DST between the 7H9 broth microdilution MIC and agar dilution MIC using either 7H10 or 7H11 agar. Therefore, MIC values obtained by the agar dilution method cannot be used interchangeably with those obtained by the 7H9 broth microdilution method.

Both the agar and broth dilution methods can be used to accurately determine bedaquiline MIC but various factors will dictate which method is selected in each laboratory. Expeditious reporting of DST results is critical to clinical decision making, particularly regarding antimycobacterial agent selection for patients infected with MDR strains. Therefore, one significant advantage of the broth microdilution method over agar dilution is that it provides DST

results in half the time, with an incubation period of 10 days or less compared with 21 days or more for agar media with the current methodologies. Of note, this comparison does not take into account the six weeks required to obtain pure colonies for the preparation of the inoculum used in either method. The bedaquiline 7H9 broth microdilution DST using frozen microtiter plates can also be performed using manual dilution (Text S2).

Limitations of the studies included the requirement to exclude from analysis the data from one laboratory (Lab-5) for the 7H10 agar dilution method, and one laboratory (Lab-1) for the 7H9 broth due to unusually high bedaquiline MICs. Although some other specific issues were reported by individual laboratories, these did not affect the outcome for determination of bedaquiline MIC ranges (Text S1). In addition, the bedaquiline MIC QC range using the broth microdilution method is not applicable to the widely used Mycobacterium Growth Indicator Tube (MGIT, Becton Dickinson) system (27), a commercial rapid liquid culture system for diagnosis and DST. Studies have been done to determine the mean bedaquiline MIC values (0.65 µg/ml) (28) or ranges (≤0.03–1.00 µg/ml) (29) and epidemiological cut-offs (1.6 µg/ml) (28) and 1.0 µg/ml (29), respectively) for MTB using the MGIT960 system. However, these studies were not tier-2, multi-laboratory, reproducibility studies, and in one of the studies (29), crushed tablets were used instead of pure powder. The authors expect that the manufacturer of the MGIT system will perform further QC studies of bedaquiline DST in the MGIT 960 system under rigorous standards.

The methodologies established in these studies for 7H10/7H11 agar dilution MIC and 7H9 broth microdilution MIC, coupled with the definition of bedaquiline MIC QC range standards, will inform future research, as well as providing guidance for routine clinical bedaquiline phenotypic DST and MTB drug resistance monitoring in laboratories worldwide.

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Transparency declarations

KK and NL are full-time employees of Janssen. The authors declare no additional financial conflicts of interest.

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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Author contributions

All authors substantially contributed to the study's design and protocol and execution of the work described. All authors were involved in the development of the primary manuscript, interpretation of the data, have read and approved the final version, and have met the criteria for authorship as established by the ICMJE.

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Supplementary Material

Text S1

Specific issues reported by the participating laboratories

Lab-1 produced only four data points that were considered outside the usual range for bedaquiline MIC against strain H37Rv. Lab-6 reported that the OADC, used in preparing the agar media, had become contaminated. The OADC was replaced with a new batch from the same supplier. Several of the laboratories did not read the MIC results at all the timepoints specified in the protocol for the broth microdilution method (days 7, 10 and 14). Some reported day 7 results as unreliable, while Lab-1 read all the results at day 7. Lab-8 read all the results at day 14. With the exception of using day 7 results for Lab-1 and Day 14 for Lab-8, all analyses used the day 10 data.

Text S2

Method for bedaquiline MIC determination using 7H9 broth medium

Preparation of bedaquiline

A 400 µg/ml working solution is made in DMSO and 2-fold serial dilutions are made from 400–1.6 µg/ml in DMSO. These working solutions are then diluted 1/100 in 7H9 medium to obtain 2X drug concentrations of 4, 2, 1, 0.5, 0.25, 0.12, 0.06, 0.03 and 0.015 µg/ml.

Preparation of MTB suspension

MTB isolates are grown on 7H11 agar medium (or Lowenstein-Jensen) and colonies resuspended in 7H9-S. The turbidity of the resulting suspension is adjusted with phosphate-buffered saline to match that of a McFarland standard 1 suspension which corresponds to ~5 X 10^7 CFU/ml of microorganisms. 2X inoculum is prepared using a calibrated micropipeting device by inoculating 14.7 ml of 7H9-S tube with 300 µl of the 1 McFarland suspensions (50-fold dilution from 1 McFarland or 1 X 10^6 CFU/ml).

Preparation and inoculation of the microtiter plates

A 100 µl of 2X bedaquiline working solutions is added to wells except the growth control wells which receive 100 µl 7H9-S only. Pour the 2X inoculum into a disposable inoculum reservoir. Using a 8 or 12 channel micro-pipette and sterile tips with filters, add 100 µl 2X inoculum 1 x 10^6 CFU/ml in 7H9-S broth to all microtiter wells, including the growth control well, but not the negative control well, which receives 100 µl of 7H9-S broth only. At this point the final drug concentrations are 2, 1, 0.5, 0.25, 0.12, 0.06, 0.03, 0.015 and 0.008 µg/ml, and the inoculum size is 5 x 10^5 CFU/ml. After inoculation, seal the plates in plastic bags and incubate at 35–37ºC.

Reading of the microtiter plates

Read MICs at day 7, day 10 and day 14. No more reading should occur after day 14. For better interpretation of the results, growth must be compared to that of the growth control well.

- Microtiter plates should be read by visual inspection per local procedure.
- The MIC of each drug is interpreted as the lowest concentration of the antibiotic that prevents visual growth. For bedaquiline, the endpoint should be assessed as a completely clear well.
- Positive and negative controls: the positive control should show positive growth and the negative control should show no growth within the incubation protocol period. If the negative control shows a growth, the procedures need to be investigated for potential cross-manipulation and all reagents checked for possible source of contamination.

Note:

1. Commercial frozen microtiter plates from Thermo Fisher could be used for liquid based MIC. In this case, the product package insert should be followed for the entire DST.
2. The 7H9-S medium should be stored protected from light at 4°C.
3. It is important to have fresh growth on a solid medium (21–28 days old). Older cultures may result in unreliable susceptibility test results.
4. Drug solutions in DMSO may be frozen in aliquots at –20°C and stored for up to 3 months. Once thawed, discard the leftover and do not store or refreeze.
5. The test plate should be in polystyrene.

Detection of contamination

The incidence of contamination can vary from laboratory to laboratory depending on several factors. The recommendation is that up to 5% contamination rate is acceptable. Liquid media are more susceptible to contamination than solid media. To prevent contamination, it is extremely important to take care during the manipulation and to work with sterile material. Any well with a turbid appearance is suspected of contamination and its result is not valid.

Quality control

For bedaquiline MIC determinations, a quality control is performed by testing the MTB H37Rv strain (a susceptible strain to bedaquiline; ATCC-American Type Culture Collection - number 27294) on each new lot of 7H9 broth using the same set of concentrations used in the assay for the MTB isolates. Standard bedaquiline solutions should provide the following range of MIC values: 0.015–0.06 µg/ml.

Table S1. 7H10 agar dilution raw data from all laboratories for bedaquiline tested against the MTB H37Rv strain

DST, drug susceptibility test; BDQ, bedaquiline; MIC, minimal inhibitory concentration; INH, isoniazid

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 1	Becton Dickinson	3116410	1	4/24/2014	0.03	0.12	Lab-1
Lot 1	Becton Dickinson	3116410	2	4/25/2014	0.06	0.12	Lab-1
Lot 1	Becton Dickinson	3116410	3	4/28/2014	0.03	0.12	Lab-1
Lot 1	Becton Dickinson	3116410	4	4/29/2014	0.03	0.12	Lab-1
Lot 1	Becton Dickinson	3116410	5	5/5/2014	0.03	0.12	Lab-1
Lot 1	Becton Dickinson	3116410	6	5/6/2014	0.03	0.12	Lab-1
Lot 1	Becton Dickinson	3116410	7	5/19/2014	0.12	0.12	Lab-1
Lot 1	Becton Dickinson	3116410	8	5/21/2014	0.12	0.12	Lab-1
Lot 1	Becton Dickinson	3116410	9	5/22/2014	0.12	0.12	Lab-1
Lot 1	Becton Dickinson	3116410	10	6/4/2014	0.12	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL7582V	1	4/24/2014	0.03	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL7582V	2	4/25/2014	0.06	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL7582V	3	4/28/2014	0.03	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL7582V	4	4/29/2014	0.03	0.06	Lab-1
Lot 2	Sigma Aldrich	BCBL7582V	5	5/5/2014	0.03	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL7582V	6	5/6/2014	0.03	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL7582V	7	5/19/2014	0.06	0.06	Lab-1
Lot 2	Sigma Aldrich	BCBL7582V	8	5/21/2014	0.12	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL7582V	9	5/22/2014	0.12	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL7582V	10	6/4/2014	0.06	0.12	Lab-1
Lot 3	Titan Biotech	M2B4KN01	1	4/24/2014	0.03	0.12	Lab-1
Lot 3	Titan Biotech	M2B4KN01	2	4/25/2014	0.06	0.06	Lab-1
Lot 3	Titan Biotech	M2B4KN01	3	4/28/2014	0.06	0.12	Lab-1
Lot 3	Titan Biotech	M2B4KN01	4	4/29/2014	0.06	0.12	Lab-1

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 3	Titan Biotech	M2B4KN01	5	5/5/2014	0.03	0.12	Lab-1
Lot 3	Titan Biotech	M2B4KN01	6	5/6/2014	0.03	0.12	Lab-1
Lot 3	Titan Biotech	M2B4KN01	7	5/19/2014	0.12	0.12	Lab-1
Lot 3	Titan Biotech	M2B4KN01	8	5/21/2014	0.12	0.12	Lab-1
Lot 3	Titan Biotech	M2B4KN01	9	5/22/2014	0.12	0.12	Lab-1
Lot 3	Titan Biotech	M2B4KN01	10	6/4/2014	0.06	0.12	Lab-1
Lot 1	Becton Dickinson	3116410	1	3/18/2014	0.03	0.06	Lab-2
Lot 1	Becton Dickinson	3116410	2	3/25/2014	0.06	0.12	Lab-2
Lot 1	Becton Dickinson	3116410	3	5/19/2014	0.015	0.12	Lab-2
Lot 1	Becton Dickinson	3116410	4	5/19/2014	0.03	0.12	Lab-2
Lot 1	Becton Dickinson	3116410	5	5/19/2014	0.03	0.12	Lab-2
Lot 1	Becton Dickinson	3116410	6	5/20/2014	0.03	0.12	Lab-2
Lot 1	Becton Dickinson	3116410	7	5/20/2014	0.03	0.12	Lab-2
Lot 1	Becton Dickinson	3116410	8	5/20/2014	0.03	0.12	Lab-2
Lot 1	Becton Dickinson	3116410	9	6/13/2014	0.03	0.25	Lab-2
Lot 1	Becton Dickinson	3116410	10	6/13/2014	0.06	0.12	Lab-2
Lot1	Becton Dickinson	3116410	11	6/13/2014	0.06	0.12	Lab-2
Lot 2	Sigma Aldrich	BCBL7582V	1	3/18/2014	0.03	0.25	Lab-2
Lot 2	Sigma Aldrich	BCBL7582V	2	3/25/2014	0.06	>0.25	Lab-2
Lot 2	Sigma Aldrich	BCBL7582V	3	5/19/2014	<=0.008	>0.25	Lab-2
Lot 2	Sigma Aldrich	BCBL7582V	4	5/19/2014	0.03	>0.25	Lab-2
Lot 2	Sigma Aldrich	BCBL7582V	5	5/19/2014	0.03	>0.25	Lab-2
Lot 2	Sigma Aldrich	BCBL7582V	6	5/20/2014	0.03	>0.25	Lab-2
Lot 2	Sigma Aldrich	BCBL7582V	7	5/20/2014	0.03	>0.25	Lab-2
Lot 2	Sigma Aldrich	BCBL7582V	8	5/20/2014	0.03	0.25	Lab-2
Lot 2	Sigma Aldrich	BCBL7582V	9	6/13/2014	0.03	>0.25	Lab-2
Lot 2	Sigma Aldrich	BCBL7582V	10	6/13/2014	0.015	>0.25	Lab-2

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 2	Sigma Aldrich	BCBL7582V	11	6/13/2014	0.03	>0.25	Lab-2
Lot 3	Titan Biotech	M2B4KN01	1	3/18/2014	0.03	0.12	Lab-2
Lot 3	Titan Biotech	M2B4KN01	2	3/25/2014	0.06	0.12	Lab-2
Lot 3	Titan Biotech	M2B4KN01	3	5/19/2014	0.015	0.12	Lab-2
Lot 3	Titan Biotech	M2B4KN01	4	5/19/2014	0.015	0.25	Lab-2
Lot 3	Titan Biotech	M2B4KN01	5	5/19/2014	0.03	0.12	Lab-2
Lot 3	Titan Biotech	M2B4KN01	6	5/20/2014	0.03	0.12	Lab-2
Lot 3	Titan Biotech	M2B4KN01	7	5/20/2014	0.03	0.12	Lab-2
Lot 3	Titan Biotech	M2B4KN01	8	5/20/2014	0.015	0.06	Lab-2
Lot 3	Titan Biotech	M2B4KN01	9	6/13/2014	0.03	0.25	Lab-2
Lot 3	Titan Biotech	M2B4KN01	10	6/13/2014	0.03	0.25	Lab-2
Lot 3	Titan Biotech	M2B4KN01	11	6/13/2014	0.03	0.12	Lab-2
Lot 1	Becton Dickinson	3116410	1	6/16/2014	0.06	0.12	Lab-3
Lot 1	Becton Dickinson	3116410	2	6/16/2014	0.06	0.12	Lab-3
Lot 1	Becton Dickinson	3116410	3	6/16/2014	0.06	0.12	Lab-3
Lot 1	Becton Dickinson	3116410	4	6/16/2014	0.06	0.12	Lab-3
Lot 1	Becton Dickinson	3116410	5	6/16/2014	0.06	0.12	Lab-3
Lot 1	Becton Dickinson	3116410	6	6/17/2014	0.06	0.12	Lab-3
Lot 1	Becton Dickinson	3116410	7	6/17/2014	0.06	0.12	Lab-3
Lot 1	Becton Dickinson	3116410	8	6/17/2014	0.06	0.12	Lab-3
Lot 1	Becton Dickinson	3116410	9	6/17/2014	0.06	0.12	Lab-3
Lot 1	Becton Dickinson	3116410	10	6/17/2014	0.06	0.12	Lab-3
Lot 2	Sigma Aldrich	BCBL7582V	1	6/30/2014	0.03	0.12	Lab-3
Lot 2	Sigma Aldrich	BCBL7582V	2	6/30/2014	0.03	0.12	Lab-3
Lot 2	Sigma Aldrich	BCBL7582V	3	6/30/2014	0.03	0.12	Lab-3
Lot 2	Sigma Aldrich	BCBL7582V	4	6/30/2014	0.03	0.12	Lab-3
Lot 2	Sigma Aldrich	BCBL7582V	5	6/30/2014	0.03	0.06	Lab-3

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 2	Sigma Aldrich	BCBL7582V	6	7/1/2014	0.03	0.12	Lab-3
Lot 2	Sigma Aldrich	BCBL7582V	7	7/1/2014	0.03	0.06	Lab-3
Lot 2	Sigma Aldrich	BCBL7582V	8	7/1/2014	0.03	0.12	Lab-3
Lot 2	Sigma Aldrich	BCBL7582V	9	7/1/2014	0.03	0.12	Lab-3
Lot 2	Sigma Aldrich	BCBL7582V	10	7/1/2014	0.03	0.06	Lab-3
Lot 3	Titan Biotech	M2B4KN01	1	8/19/2014	0.12	0.12	Lab-3
Lot 3	Titan Biotech	M2B4KN01	2	8/19/2014	0.12	0.12	Lab-3
Lot 3	Titan Biotech	M2B4KN01	3	8/19/2014	0.06	0.12	Lab-3
Lot 3	Titan Biotech	M2B4KN01	4	8/19/2014	0.06	0.12	Lab-3
Lot 3	Titan Biotech	M2B4KN01	5	8/19/2014	0.12	0.12	Lab-3
Lot 3	Titan Biotech	M2B4KN01	6	8/20/2014	0.12	0.12	Lab-3
Lot 3	Titan Biotech	M2B4KN01	7	8/20/2014	0.12	0.12	Lab-3
Lot 3	Titan Biotech	M2B4KN01	8	8/20/2014	0.12	0.12	Lab-3
Lot 3	Titan Biotech	M2B4KN01	9	8/20/2014	0.12	0.12	Lab-3
Lot 3	Titan Biotech	M2B4KN01	10	8/20/2014	0.12	0.12	Lab-3
Lot 1	Becton Dickinson	3116410	1	5/28/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3116410	2	5/28/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3116410	3	5/28/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3116410	4	5/28/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3116410	5	5/28/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3116410	6	5/28/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3116410	7	5/28/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3116410	8	5/28/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3116410	9	5/28/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3116410	10	5/28/2014	0.06	0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL7582V	1	9/11/2014	0.06	>0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL7582V	2	9/11/2014	0.06	>0.12	Lab-4

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 2	Sigma Aldrich	BCBL7582V	3	9/11/2014	0.06	>0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL7582V	4	9/11/2014	0.06	>0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL7582V	5	9/11/2014	0.06	>0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL7582V	6	9/11/2014	0.06	>0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL7582V	7	9/11/2014	0.06	>0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL7582V	8	9/11/2014	0.06	>0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL7582V	9	9/11/2014	0.06	>0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL7582V	10	9/11/2014	0.06	>0.12	Lab-4
Lot 3	Titan Biotech	M2B4KN01	1	8/28/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M2B4KN01	2	8/28/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M2B4KN01	3	8/28/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M2B4KN01	4	8/28/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M2B4KN01	5	8/28/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M2B4KN01	6	8/28/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M2B4KN01	7	8/28/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M2B4KN01	8	8/28/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M2B4KN01	9	8/28/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M2B4KN01	10	8/28/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3116410	1	9/12/2014	0.25	0.12	Lab-5
Lot 1	Becton Dickinson	3116410	2	9/12/2014	0.25	0.12	Lab-5
Lot 1	Becton Dickinson	3116410	3	9/12/2014	0.25	0.12	Lab-5
Lot 1	Becton Dickinson	3116410	4	9/12/2014	0.12	0.12	Lab-5
Lot 1	Becton Dickinson	3116410	5	9/12/2014	0.25	0.12	Lab-5
Lot 1	Becton Dickinson	3116410	6	9/12/2014	0.25	0.12	Lab-5
Lot 1	Becton Dickinson	3116410	7	9/12/2014	0.25	0.12	Lab-5
Lot 1	Becton Dickinson	3116410	8	9/12/2014	0.25	0.12	Lab-5
Lot 1	Becton Dickinson	3116410	9	9/12/2014	0.25	0.12	Lab-5

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 1	Becton Dickinson	3116410	10	9/12/2014	0.25	0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL7582V	1	8/4/2014	0.015	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL7582V	2	8/4/2014	0.015	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL7582V	3	8/4/2014	0.008	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL7582V	4	8/4/2014	0.03	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL7582V	5	8/4/2014	0.03	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL7582V	6	8/4/2014	0.03	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL7582V	7	8/4/2014	0.03	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL7582V	8	8/4/2014	0.06	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL7582V	9	8/4/2014	0.03	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL7582V	10	8/4/2014	0.03	>0.12	Lab-5
Lot 3	Titan Biotech	M2B4KN01	1	8/7/2014	0.008	>0.12	Lab-5
Lot 3	Titan Biotech	M2B4KN01	2	8/7/2014	0.015	>0.12	Lab-5
Lot 3	Titan Biotech	M2B4KN01	3	8/7/2014	0.015	>0.12	Lab-5
Lot 3	Titan Biotech	M2B4KN01	4	8/7/2014	0.015	>0.12	Lab-5
Lot 3	Titan Biotech	M2B4KN01	5	8/7/2014	0.015	>0.12	Lab-5
Lot 3	Titan Biotech	M2B4KN01	6	8/7/2014	0.015	>0.12	Lab-5
Lot 3	Titan Biotech	M2B4KN01	7	8/7/2014	0.008	>0.12	Lab-5
Lot 3	Titan Biotech	M2B4KN01	8	8/7/2014	0.008	>0.12	Lab-5
Lot 3	Titan Biotech	M2B4KN01	9	8/7/2014	0.015	>0.12	Lab-5
Lot 3	Titan Biotech	M2B4KN01	10	8/7/2014	0.015	>0.12	Lab-5
Lot 1	Becton Dickinson	3116410	1	7/9/2014	0.03	0.12	Lab-6
Lot 1	Becton Dickinson	3116410	2	7/10/2014	0.03	0.12	Lab-6
Lot 1	Becton Dickinson	3116410	3	7/11/2014	0.03	0.12	Lab-6
Lot 1	Becton Dickinson	3116410	4	7/12/2014	0.03	0.12	Lab-6
Lot 1	Becton Dickinson	3116410	5	7/14/2014	0.03	0.12	Lab-6
Lot 1	Becton Dickinson	3116410	6	7/15/2014	0.03	0.12	Lab-6

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 1	Becton Dickinson	3116410	7	7/16/2014	0.03	0.12	Lab-6
Lot 1	Becton Dickinson	3116410	8	7/17/2014	0.03	0.12	Lab-6
Lot 1	Becton Dickinson	3116410	9	7/18/2014	0.03	0.12	Lab-6
Lot 1	Becton Dickinson	3116410	10	7/19/2014	0.03	0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL7582V	1	7/21/2014	0.03	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL7582V	2	7/22/2014	0.03	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL7582V	3	7/23/2014	0.015	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL7582V	4	7/24/2014	≤ 0.008	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL7582V	5	7/24/2014	≤ 0.008	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL7582V	6	7/28/2014	≤ 0.008	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL7582V	7	7/29/2014	≤ 0.008	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL7582V	8	7/30/2014	0.015	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL7582V	9	7/31/2014	≤ 0.008	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL7582V	10	8/1/2014	≤ 0.008	> 0.12	Lab-6
Lot 3	Titan Biotech	M2B4KN01	1	8/2/2014	0.03	> 0.12	Lab-6
Lot 3	Titan Biotech	M2B4KN01	2	8/3/2014	0.015	0.12	Lab-6
Lot 3	Titan Biotech	M2B4KN01	3	8/4/2014	0.015	0.12	Lab-6
Lot 3	Titan Biotech	M2B4KN01	4	8/5/2014	0.015	> 0.12	Lab-6
Lot 3	Titan Biotech	M2B4KN01	5	8/6/2014	0.015	> 0.12	Lab-6
Lot 3	Titan Biotech	M2B4KN01	6	8/7/2014	0.015	> 0.12	Lab-6
Lot 3	Titan Biotech	M2B4KN01	7	8/8/2014	0.03	> 0.12	Lab-6
Lot 3	Titan Biotech	M2B4KN01	8	8/9/2014	0.015	> 0.12	Lab-6
Lot 3	Titan Biotech	M2B4KN01	9	8/11/2014	0.015	> 0.12	Lab-6
Lot 3	Titan Biotech	M2B4KN01	10	8/12/2014	0.015	> 0.12	Lab-6
Lot 1	Becton Dickinson	3116410	1	09/25/14	0.03	0.12	Lab-7
Lot 1	Becton Dickinson	3116410	2	09/26/14	0.03	0.12	Lab-7
Lot 1	Becton Dickinson	3116410	3	09/26/14	0.06	0.12	Lab-7

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 1	Becton Dickinson	3116410	4	09/27/14	0.06	0.12	Lab-7
Lot 1	Becton Dickinson	3116410	5	09/28/14	0.06	0.12	Lab-7
Lot 1	Becton Dickinson	3116410	6	09/28/14	0.03	0.12	Lab-7
Lot 1	Becton Dickinson	3116410	7	09/28/14	0.03	0.12	Lab-7
Lot 1	Becton Dickinson	3116410	8	09/29/14	0.03	0.12	Lab-7
Lot 1	Becton Dickinson	3116410	9	09/30/12	0.06	0.12	Lab-7
Lot 1	Becton Dickinson	3116410	10	10/01/14	0.06	0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL7582V	1	09/25/14	0.03	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL7582V	2	09/26/14	0.03	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL7582V	3	09/26/14	0.03	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL7582V	4	09/27/14	0.03	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL7582V	5	09/28/14	0.03	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL7582V	6	09/28/14	0.06	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL7582V	7	09/28/14	0.03	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL7582V	8	09/29/14	0.06	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL7582V	9	09/30/12	0.25*	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL7582V	10	10/01/14	0.03	>0.12	Lab-7
Lot 3	Titan Biotech	M2B4KN01	1	09/25/14	0.015	>0.12	Lab-7
Lot 3	Titan Biotech	M2B4KN01	2	09/26/14	0.015	0.12	Lab-7
Lot 3	Titan Biotech	M2B4KN01	3	09/26/14	0.06	>0.12	Lab-7
Lot 3	Titan Biotech	M2B4KN01	4	09/27/14	0.06	0.12	Lab-7
Lot 3	Titan Biotech	M2B4KN01	5	09/28/14	0.015	0.12	Lab-7
Lot 3	Titan Biotech	M2B4KN01	6	09/28/14	0.015	0.12	Lab-7
Lot 3	Titan Biotech	M2B4KN01	7	09/28/14	0.015	0.12	Lab-7
Lot 3	Titan Biotech	M2B4KN01	8	09/29/14	0.015	0.12	Lab-7
Lot 3	Titan Biotech	M2B4KN01	9	09/30/12	0.015	0.12	Lab-7
Lot 3	Titan Biotech	M2B4KN01	10	10/01/14	0.015	0.12	Lab-7

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 1	Becton Dickinson	3116410	1	8/18/14	0.06		Lab-8
Lot 1	Becton Dickinson	3116410	2	8/25/14	0.06		Lab-8
Lot 1	Becton Dickinson	3116410	3	9/2/14	0.06		Lab-8
Lot 1	Becton Dickinson	3116410	4	9/4/14	0.06		Lab-8
Lot 1	Becton Dickinson	3116410	5	9/17/14	0.06		Lab-8
Lot 1	Becton Dickinson	3116410	6	9/29/14	0.25		Lab-8
Lot 1	Becton Dickinson	3116410	7	10/06/14	0.06		Lab-8
Lot 1	Becton Dickinson	3116410	8	10/14/14	0.06		Lab-8
Lot 1	Becton Dickinson	3116410	9	10/14/14	0.12		Lab-8
Lot 1	Becton Dickinson	3116410	10	10/20/14	0.12		Lab-8
Lot 2	Sigma Aldrich	BCBL7582V	1	8/18/14	0.03		Lab-8
Lot 2	Sigma Aldrich	BCBL7582V	2	8/25/14	0.03		Lab-8
Lot 2	Sigma Aldrich	BCBL7582V	3	9/2/14	0.03		Lab-8
Lot 2	Sigma Aldrich	BCBL7582V	4	9/4/14	0.03		Lab-8
Lot 2	Sigma Aldrich	BCBL7582V	5	9/17/14	0.06		Lab-8
Lot 2	Sigma Aldrich	BCBL7582V	6	9/29/14	0.03		Lab-8
Lot 2	Sigma Aldrich	BCBL7582V	7	10/06/14	0.06		Lab-8
Lot 2	Sigma Aldrich	BCBL7582V	8	10/14/14	0.03		Lab-8
Lot 2	Sigma Aldrich	BCBL7582V	9	10/14/14	0.06		Lab-8
Lot 2	Sigma Aldrich	BCBL7582V	10	10/20/14	0.06		Lab-8
Lot 3	Titan Biotech	M2B4KN01	1	8/18/14	0.06		Lab-8
Lot 3	Titan Biotech	M2B4KN01	2	8/25/14	0.06		Lab-8
Lot 3	Titan Biotech	M2B4KN01	3	9/2/14	0.06		Lab-8
Lot 3	Titan Biotech	M2B4KN01	4	9/4/14	0.03		Lab-8
Lot 3	Titan Biotech	M2B4KN01	5	9/17/14	0.06		Lab-8
Lot 3	Titan Biotech	M2B4KN01	6	9/29/14	0.03		Lab-8
Lot 3	Titan Biotech	M2B4KN01	7	10/06/14	0.06		Lab-8

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 3	Titan Biotech	M2B4KN01	8	10/14/14	0.06		Lab-8
Lot 3	Titan Biotech	M2B4KN01	9	10/14/14	0.12		Lab-8
Lot 3	Titan Biotech	M2B4KN01	10	10/20/14	0.12		Lab-8

Table S2. 7H11 agar dilution raw data from all laboratories for bedaquiline tested against the MTB H37Rv strain

DST, drug susceptibility test; BDQ, bedaquiline; MIC, minimal inhibitory concentration; INH, isoniazid

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 1	Becton Dickinson	3189213	1	4/24/2014	0.03	0.12	Lab-1
Lot 1	Becton Dickinson	3189213	2	4/25/2014	0.06	0.12	Lab-1
Lot 1	Becton Dickinson	3189213	3	4/28/2014	0.06	0.12	Lab-1
Lot 1	Becton Dickinson	3189213	4	4/29/2014	0.03	0.12	Lab-1
Lot 1	Becton Dickinson	3189213	5	5/5/2014	0.03	0.06	Lab-1
Lot 1	Becton Dickinson	3189213	6	5/6/2014	0.015	0.12	Lab-1
Lot 1	Becton Dickinson	3189213	7	5/19/2014	0.12	0.12	Lab-1
Lot 1	Becton Dickinson	3189213	8	5/21/2014	0.12	0.12	Lab-1
Lot 1	Becton Dickinson	3189213	9	5/22/2014	0.06	0.12	Lab-1
Lot 1	Becton Dickinson	3189213	10	6/4/2014	0.12	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL4307V	1	4/24/2014	0.03	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL4307V	2	4/25/2014	0.03	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL4307V	3	4/28/2014	0.03	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL4307V	4	4/29/2014	0.06	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL4307V	5	5/5/2014	0.03	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL4307V	6	5/6/2014	0.03	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL4307V	7	5/19/2014	0.06	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL4307V	8	5/21/2014	0.06	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL4307V	9	5/22/2014	0.12	0.12	Lab-1
Lot 2	Sigma Aldrich	BCBL4307V	10	6/4/2014	0.12	0.12	Lab-1
Lot 3	Titan Biotech	M7I6KN01	1	4/24/2014	0.03	0.12	Lab-1
Lot 3	Titan Biotech	M7I6KN01	2	4/25/2014	0.03	0.12	Lab-1
Lot 3	Titan Biotech	M7I6KN01	3	4/28/2014	0.06	0.06	Lab-1
Lot 3	Titan Biotech	M7I6KN01	4	4/29/2014	0.03	0.12	Lab-1

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 3	Titan Biotech	M7I6KN01	5	5/5/2014	0.03	0.12	Lab-1
Lot 3	Titan Biotech	M7I6KN01	6	5/6/2014	0.06	0.12	Lab-1
Lot 3	Titan Biotech	M7I6KN01	7	5/19/2014	0.06	0.12	Lab-1
Lot 3	Titan Biotech	M7I6KN01	8	5/21/2014	0.12	0.12	Lab-1
Lot 3	Titan Biotech	M7I6KN01	9	5/22/2014	0.06	0.12	Lab-1
Lot 3	Titan Biotech	M7I6KN01	10	6/4/2014	0.06	0.12	Lab-1
Lot 1	Becton Dickinson	3189213	1	3/18/2014	0.06	0.03	Lab-2
Lot 1	Becton Dickinson	3189213	2	3/25/2014	0.03	0.12	Lab-2
Lot 1	Becton Dickinson	3189213	3	5/19/2014	0.03	0.12	Lab-2
Lot 1	Becton Dickinson	3189213	4	5/19/2014	0.03	0.12	Lab-2
Lot 1	Becton Dickinson	3189213	5	5/19/2014	0.03	0.12	Lab-2
Lot 1	Becton Dickinson	3189213	6	5/20/2014	0.03	0.12	Lab-2
Lot 1	Becton Dickinson	3189213	7	5/20/2014	0.03	0.003	Lab-2
Lot 1	Becton Dickinson	3189213	8	5/20/2014	0.03	0.12	Lab-2
Lot 1	Becton Dickinson	3189213	9	6/13/2014	0.06	0.12	Lab-2
Lot 1	Becton Dickinson	3189213	10	6/13/2014	0.03	0.12	Lab-2
Lot 1	Becton Dickinson	3189213	11	6/13/2014	0.03	0.12	Lab-2
Lot 2	Sigma Aldrich	BCBL4307V	1	3/18/2014	0.03	0.12	Lab-2
Lot 2	Sigma Aldrich	BCBL4307V	2	3/25/2014	0.06	>0.25	Lab-2
Lot 2	Sigma Aldrich	BCBL4307V	3	5/19/2014	0.03	>0.25	Lab-2
Lot 2	Sigma Aldrich	BCBL4307V	4	5/19/2014	0.03	>0.25	Lab-2
Lot 2	Sigma Aldrich	BCBL4307V	5	5/19/2014	0.03	>0.25	Lab-2
Lot 2	Sigma Aldrich	BCBL4307V	6	5/20/2014	0.015	0.03	Lab-2
Lot 2	Sigma Aldrich	BCBL4307V	7	5/20/2014	0.03	>0.25	Lab-2
Lot 2	Sigma Aldrich	BCBL4307V	8	5/20/2014	0.03	>0.25	Lab-2
Lot 2	Sigma Aldrich	BCBL4307V	9	6/13/2014	0.03	>0.25	Lab-2
Lot 2	Sigma Aldrich	BCBL4307V	10	6/13/2014	0.03	>0.25	Lab-2

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 2	Sigma Aldrich	BCBL4307V	11	6/13/2014	0.03	>0.25	Lab-2
Lot 3	Titan Biotech	M7I6KN01	1	3/18/2014	0.03	0.06	Lab-2
Lot 3	Titan Biotech	M7I6KN01	2	3/25/2014	0.03	0.25	Lab-2
Lot 3	Titan Biotech	M7I6KN01	3	5/19/2014	<0.008	0.12	Lab-2
Lot 3	Titan Biotech	M7I6KN01	4	5/19/2014	0.03	0.12	Lab-2
Lot 3	Titan Biotech	M7I6KN01	6	5/20/2014	0.015	0.06	Lab-2
Lot 3	Titan Biotech	M7I6KN01	7	5/20/2014	0.03	0.03	Lab-2
Lot 3	Titan Biotech	M7I6KN01	8	5/20/2014	0.03	0.12	Lab-2
Lot 3	Titan Biotech	M7I6KN01	9	6/13/2014	0.03	0.25	Lab-2
Lot 3	Titan Biotech	M7I6KN01	10	6/13/2014	0.015	0.25	Lab-2
Lot 3	Titan Biotech	M7I6KN01	11	6/13/2014	0.03	0.12	Lab-2
Lot 1	Becton Dickinson	3189213	1	6/16/2014	0.03	0.12	Lab-3
Lot 1	Becton Dickinson	3189213	2	6/16/2014	0.03	0.12	Lab-3
Lot 1	Becton Dickinson	3189213	3	6/16/2014	0.03	0.06	Lab-3
Lot 1	Becton Dickinson	3189213	4	6/16/2014	0.03	0.06	Lab-3
Lot 1	Becton Dickinson	3189213	5	6/16/2014	0.03	0.06	Lab-3
Lot 1	Becton Dickinson	3189213	6	6/17/2014	0.03	0.12	Lab-3
Lot 1	Becton Dickinson	3189213	7	6/17/2014	0.03	0.06	Lab-3
Lot 1	Becton Dickinson	3189213	8	6/17/2014	0.03	0.12	Lab-3
Lot 1	Becton Dickinson	3189213	9	6/17/2014	0.06	0.12	Lab-3
Lot 1	Becton Dickinson	3189213	10	6/17/2014	0.06	0.12	Lab-3
Lot 2	Sigma Aldrich	BCBL4307V	1	6/30/2014	0.03	0.12	Lab-3
Lot 2	Sigma Aldrich	BCBL4307V	2	6/30/2014	0.03	0.06	Lab-3
Lot 2	Sigma Aldrich	BCBL4307V	3	6/30/2014	0.03	0.12	Lab-3
Lot 2	Sigma Aldrich	BCBL4307V	4	6/30/2014	0.03	0.12	Lab-3
Lot 2	Sigma Aldrich	BCBL4307V	5	6/30/2014	0.03	0.12	Lab-3
Lot 2	Sigma Aldrich	BCBL4307V	6	7/1/2014	0.06	0.12	Lab-3

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 2	Sigma Aldrich	BCBL4307V	7	7/1/2014	0.06	0.12	Lab-3
Lot 2	Sigma Aldrich	BCBL4307V	8	7/1/2014	0.06	0.12	Lab-3
Lot 2	Sigma Aldrich	BCBL4307V	9	7/1/2014	0.06	0.06	Lab-3
Lot 2	Sigma Aldrich	BCBL4307V	10	7/1/2014	0.06	0.12	Lab-3
Lot 3	Titan Biotech	M7I6KN01	1	8/19/2014	0.03	0.12	Lab-3
Lot 3	Titan Biotech	M7I6KN01	2	8/19/2014	0.03	0.12	Lab-3
Lot 3	Titan Biotech	M7I6KN01	3	8/19/2014	0.03	0.12	Lab-3
Lot 3	Titan Biotech	M7I6KN01	4	8/19/2014	0.03	0.12	Lab-3
Lot 3	Titan Biotech	M7I6KN01	5	8/19/2014	0.03	0.12	Lab-3
Lot 3	Titan Biotech	M7I6KN01	6	8/20/2014	0.03	0.12	Lab-3
Lot 3	Titan Biotech	M7I6KN01	7	8/20/2014	0.03	0.12	Lab-3
Lot 3	Titan Biotech	M7I6KN01	8	8/20/2014	0.03	0.12	Lab-3
Lot 3	Titan Biotech	M7I6KN01	9	8/20/2014	0.03	0.12	Lab-3
Lot 3	Titan Biotech	M7I6KN01	10	8/20/2014	0.03	0.12	Lab-3
Lot 1	Becton Dickinson	3189213	1	7/31/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3189213	2	7/31/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3189213	3	7/31/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3189213	4	7/31/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3189213	5	7/31/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3189213	6	7/31/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3189213	7	7/31/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3189213	8	7/31/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3189213	9	7/31/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3189213	10	7/31/2014	0.06	0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL4307V	1	8/21/2014	0.06	>0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL4307V	2	8/21/2014	0.06	>0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL4307V	3	8/21/2014	0.06	>0.12	Lab-4

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 2	Sigma Aldrich	BCBL4307V	4	8/21/2014	0.06	>0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL4307V	5	8/21/2014	0.06	>0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL4307V	6	8/21/2014	0.06	>0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL4307V	7	8/21/2014	0.06	>0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL4307V	8	8/21/2014	0.06	>0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL4307V	9	8/21/2014	0.06	>0.12	Lab-4
Lot 2	Sigma Aldrich	BCBL4307V	10	8/21/2014	0.06	>0.12	Lab-4
Lot 3	Titan Biotech	M7I6KN01	1	9/3/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M7I6KN01	2	9/3/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M7I6KN01	3	9/3/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M7I6KN01	4	9/3/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M7I6KN01	5	9/3/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M7I6KN01	6	9/3/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M7I6KN01	7	9/3/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M7I6KN01	8	9/3/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M7I6KN01	9	9/3/2014	0.06	0.12	Lab-4
Lot 3	Titan Biotech	M7I6KN01	10	9/3/2014	0.06	0.12	Lab-4
Lot 1	Becton Dickinson	3189213	1	8/29/2014	0.06	0.12	Lab-5
Lot 1	Becton Dickinson	3189213	2	8/29/2014	0.06	0.12	Lab-5
Lot 1	Becton Dickinson	3189213	3	8/29/2014	0.12	0.12	Lab-5
Lot 1	Becton Dickinson	3189213	4	8/29/2014	0.12	0.12	Lab-5
Lot 1	Becton Dickinson	3189213	5	8/29/2014	0.06	0.12	Lab-5
Lot 1	Becton Dickinson	3189213	6	8/29/2014	0.06	0.12	Lab-5
Lot 1	Becton Dickinson	3189213	7	8/29/2014	0.06	0.12	Lab-5
Lot 1	Becton Dickinson	3189213	8	8/29/2014	0.06	0.12	Lab-5
Lot 1	Becton Dickinson	3189213	9	8/29/2014	0.06	0.12	Lab-5
Lot 1	Becton Dickinson	3189213	10	8/29/2014	0.03	0.12	Lab-5

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 2	Sigma Aldrich	BCBL4307V	1	9/10/2014	0.25	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL4307V	2	9/10/2014	0.12	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL4307V	3	9/10/2014	0.25	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL4307V	4	9/10/2014	0.25	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL4307V	5	9/10/2014	0.25	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL4307V	6	9/10/2014	0.25	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL4307V	7	9/10/2014	0.25	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL4307V	8	9/10/2014	0.25	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL4307V	9	9/10/2014	0.25	>0.12	Lab-5
Lot 2	Sigma Aldrich	BCBL4307V	10	9/10/2014	0.25	>0.12	Lab-5
Lot 3	Titan Biotech	M7I6KN01	1	9/5/2014	0.12	0.12	Lab-5
Lot 3	Titan Biotech	M7I6KN01	2	9/5/2014	0.06	0.12	Lab-5
Lot 3	Titan Biotech	M7I6KN01	3	9/5/2014	0.06	0.12	Lab-5
Lot 3	Titan Biotech	M7I6KN01	4	9/5/2014	0.06	0.12	Lab-5
Lot 3	Titan Biotech	M7I6KN01	5	9/5/2014	0.03	0.12	Lab-5
Lot 3	Titan Biotech	M7I6KN01	6	9/5/2014	0.12	0.12	Lab-5
Lot 3	Titan Biotech	M7I6KN01	7	9/5/2014	0.03	0.12	Lab-5
Lot 3	Titan Biotech	M7I6KN01	8	9/5/2014	0.06	0.12	Lab-5
Lot 3	Titan Biotech	M7I6KN01	9	9/5/2014	0.06	0.12	Lab-5
Lot 3	Titan Biotech	M7I6KN01	10	9/5/2014	0.06	0.12	Lab-5
Lot 1	Becton Dickinson	3189213	1	8/13/2014	0.06	> 0.12	Lab-6
Lot 1	Becton Dickinson	3189213	2	8/14/2014	0.06	> 0.12	Lab-6
Lot 1	Becton Dickinson	3189213	3	8/18/2014	0.06	> 0.12	Lab-6
Lot 1	Becton Dickinson	3189213	4	8/19/2014	0.06	> 0.12	Lab-6
Lot 1	Becton Dickinson	3189213	5	8/20/2014	0.06	> 0.12	Lab-6
Lot 1	Becton Dickinson	3189213	6	8/21/2014	0.06	> 0.12	Lab-6
Lot 1	Becton Dickinson	3189213	7	8/22/2014	0.06	> 0.12	Lab-6

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 1	Becton Dickinson	3189213	8	8/25/2014	0.06	> 0.12	Lab-6
Lot 1	Becton Dickinson	3189213	9	8/26/2014	0.03	> 0.12	Lab-6
Lot 1	Becton Dickinson	3189213	10	8/27/2014	0.06	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL4307V	1	9/18/2014	0.015	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL4307V	2	9/18/2014	0.015	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL4307V	3	9/18/2014	0.015	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL4307V	4	9/18/2014	0.015	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL4307V	5	9/18/2014	0.015	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL4307V	6	9/19/2014	0.015	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL4307V	7	9/19/2014	0.015	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL4307V	8	9/19/2014	0.015	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL4307V	9	9/20/2014	0.015	> 0.12	Lab-6
Lot 2	Sigma Aldrich	BCBL4307V	10	9/20/2014	0.015	> 0.12	Lab-6
Lot 3	Titan Biotech	M7I6KN01	1	9/25/2014	0.03	0.12	Lab-6
Lot 3	Titan Biotech	M7I6KN01	2	9/25/2014	0.03	0.12	Lab-6
Lot 3	Titan Biotech	M7I6KN01	3	9/25/2014	0.03	0.12	Lab-6
Lot 3	Titan Biotech	M7I6KN01	4	9/26/2014	0.03	0.12	Lab-6
Lot 3	Titan Biotech	M7I6KN01	5	9/26/2014	0.03	0.12	Lab-6
Lot 3	Titan Biotech	M7I6KN01	6	9/27/2014	0.015	0.12	Lab-6
Lot 3	Titan Biotech	M7I6KN01	7	9/27/2014	0.03	0.12	Lab-6
Lot 3	Titan Biotech	M7I6KN01	8	9/27/2014	0.015	0.12	Lab-6
Lot 3	Titan Biotech	M7I6KN01	9	9/28/2014	0.015	0.12	Lab-6
Lot 3	Titan Biotech	M7I6KN01	10	9/28/2014	0.03	0.12	Lab-6
Lot 1	Becton Dickinson	3189213	1	09/25/14	0.03	0.12	Lab-7
Lot 1	Becton Dickinson	3189213	2	09/26/14	0.03	0.12	Lab-7
Lot 1	Becton Dickinson	3189213	3	09/26/14	0.03	0.12	Lab-7
Lot 1	Becton Dickinson	3189213	4	09/27/14	0.03	0.12	Lab-7

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 1	Becton Dickinson	3189213	5	09/28/14	0.06	0.12	Lab-7
Lot 1	Becton Dickinson	3189213	6	09/28/14	0.06	0.12	Lab-7
Lot 1	Becton Dickinson	3189213	7	09/28/14	0.03	0.12	Lab-7
Lot 1	Becton Dickinson	3189213	8	09/29/14	0.06	0.12	Lab-7
Lot 1	Becton Dickinson	3189213	9	09/30/12	0.06	0.12	Lab-7
Lot 1	Becton Dickinson	3189213	10	10/01/14	0.06	0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL4307V	1	09/25/14	0.03	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL4307V	2	09/26/14	0.03	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL4307V	3	09/26/14	0.03	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL4307V	4	09/27/14	0.03	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL4307V	5	09/28/14	0.06	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL4307V	6	09/28/14	0.03	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL4307V	7	09/28/14	0.03	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL4307V	8	09/29/14	0.03	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL4307V	9	09/30/12	0.06	>0.12	Lab-7
Lot 2	Sigma Aldrich	BCBL4307V	10	10/01/14	0.06	>0.12	Lab-7
Lot 3	Titan Biotech	M7I6KN01	1	09/25/14	0.015	>0.12	Lab-7
Lot 3	Titan Biotech	M7I6KN01	2	09/26/14	0.015	>0.12	Lab-7
Lot 3	Titan Biotech	M7I6KN01	3	09/26/14	0.015	>0.12	Lab-7
Lot 3	Titan Biotech	M7I6KN01	4	09/27/14	0.015	>0.12	Lab-7
Lot 3	Titan Biotech	M7I6KN01	5	09/28/14	0.015	0.12	Lab-7
Lot 3	Titan Biotech	M7I6KN01	6	09/28/14	0.015	0.12	Lab-7
Lot 3	Titan Biotech	M7I6KN01	7	09/28/14	0.015	0.12	Lab-7
Lot 3	Titan Biotech	M7I6KN01	8	09/29/14	0.015	0.12	Lab-7
Lot 3	Titan Biotech	M7I6KN01	9	09/30/12	0.015	0.12	Lab-7
Lot 3	Titan Biotech	M7I6KN01	10	10/01/14	0.015	0.12	Lab-7
Lot 1	Becton Dickinson	3189213	1	8/18/14	0.03	0.12	Lab-8

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 1	Becton Dickinson	3189213	2	8/25/14	0.06	0.12	Lab-8
Lot 1	Becton Dickinson	3189213	3	9/2/14	0.06	>0.12	Lab-8
Lot 1	Becton Dickinson	3189213	4	9/4/14	0.03	0.12	Lab-8
Lot 1	Becton Dickinson	3189213	5	9/17/14	0.06	>0.12	Lab-8
Lot 1	Becton Dickinson	3189213	6	9/29/14	0.06	>0.12	Lab-8
Lot 1	Becton Dickinson	3189213	7	10/06/14	0.06	0.12	Lab-8
Lot 1	Becton Dickinson	3189213	8	10/14/14	0.06	0.12	Lab-8
Lot 1	Becton Dickinson	3189213	9	10/14/14	0.06	>0.12	Lab-8
Lot 1	Becton Dickinson	3189213	10	10/20/14	0.06	0.12	Lab-8
Lot 2	Sigma Aldrich	BCBL4307V	1	8/18/14	0.06		Lab-8
Lot 2	Sigma Aldrich	BCBL4307V	2	8/25/14	0.06		Lab-8
Lot 2	Sigma Aldrich	BCBL4307V	3	9/2/14	0.06		Lab-8
Lot 2	Sigma Aldrich	BCBL4307V	4	9/4/14	0.06		Lab-8
Lot 2	Sigma Aldrich	BCBL4307V	5	9/17/14	0.06		Lab-8
Lot 2	Sigma Aldrich	BCBL4307V	6	9/29/14	0.06		Lab-8
Lot 2	Sigma Aldrich	BCBL4307V	7	10/06/14	0.06		Lab-8
Lot 2	Sigma Aldrich	BCBL4307V	8	10/14/14	0.06		Lab-8
Lot 2	Sigma Aldrich	BCBL4307V	9	10/14/14	0.12		Lab-8
Lot 2	Sigma Aldrich	BCBL4307V	10	10/20/14	0.06		Lab-8
Lot 3	Titan Biotech	M7I6KN01	1	8/18/14	0.03		Lab-8
Lot 3	Titan Biotech	M7I6KN01	2	8/25/14	0.06		Lab-8
Lot 3	Titan Biotech	M7I6KN01	3	9/2/14	0.06		Lab-8
Lot 3	Titan Biotech	M7I6KN01	4	9/4/14	0.03		Lab-8
Lot 3	Titan Biotech	M7I6KN01	5	9/17/14	0.06		Lab-8
Lot 3	Titan Biotech	M7I6KN01	6	9/29/14	0.03		Lab-8
Lot 3	Titan Biotech	M7I6KN01	7	10/06/14	0.06		Lab-8
Lot 3	Titan Biotech	M7I6KN01	8	10/14/14	0.06		Lab-8

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Lab ID
Lot 3	Titan Biotech	M7I6KN01	9	10/14/14	0.06		Lab-8
Lot 3	Titan Biotech	M7I6KN01	10	10/20/14	0.06		Lab-8

Table S3. 7H9 broth microdilution raw data from all laboratories for bedaquiline tested against the MTB H37Rv strain

DST, drug susceptibility test; BDQ, bedaquiline; MIC, minimal inhibitory concentration; INH, isoniazid

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Day Read	Lab ID
Lot 1	Thermo Fisher	14181	1	7/1/2014	0.06	0.06	7	Lab-1
Lot 1	Thermo Fisher	14181	2	7/2/2014	0.25	1	7	Lab-1
Lot 1	Thermo Fisher	14181	3	7/7/2014	0.12	>1	7	Lab-1
Lot 1	Thermo Fisher	14181	4	7/9/2014	0.03	0.06	7	Lab-1
Lot 1	Thermo Fisher	14181	5	7/14/2014	0.016	0.06	7	Lab-1
Lot 1	Thermo Fisher	14181	6	7/16/2014	0.03	0.5	7	Lab-1
Lot 1	Thermo Fisher	14181	7	7/17/2014	0.5	1	7	Lab-1
Lot 1	Thermo Fisher	14181	8	7/23/2014	0.03	0.12	7	Lab-1
Lot 1	Thermo Fisher	14181	9	7/24/2014	0.03	0.25	7	Lab-1
Lot 1	Thermo Fisher	14181	10	7/25/2014	0.25	0.12	7	Lab-1
Lot 1	Thermo Fisher	14181	11	7/29/2014	0.016	0.5	7	Lab-1
Lot 1	Thermo Fisher	14181	12	7/30/2014	0.03	0.12	7	Lab-1
Lot 2	Thermo Fisher	14202	1	7/1/2014	0.016	0.06	7	Lab-1
Lot 2	Thermo Fisher	14202	2	7/2/2014	0.06	0.25	7	Lab-1
Lot 2	Thermo Fisher	14202	3	7/7/2014	0.12	0.06	7	Lab-1
Lot 2	Thermo Fisher	14202	4	7/9/2014	0.016	0.12	7	Lab-1
Lot 2	Thermo Fisher	14202	5	7/14/2014	0.016	0.25	7	Lab-1
Lot 2	Thermo Fisher	14202	6	7/16/2014	0.03	0.12	7	Lab-1
Lot 2	Thermo Fisher	14202	7	7/17/2014	0.016	0.06	7	Lab-1
Lot 2	Thermo Fisher	14202	8	7/23/2014	0.03	0.5	7	Lab-1
Lot 2	Thermo Fisher	14202	9	7/24/2014	0.016	0.06	7	Lab-1
Lot 2	Thermo Fisher	14202	10	7/25/2014	0.25	0.5	7	Lab-1
Lot 2	Thermo Fisher	14202	11	7/29/2014	0.12	0.12	7	Lab-1
Lot 2	Thermo Fisher	14202	12	7/30/2014	0.016	0.5	7	Lab-1

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Day Read	Lab ID
Lot 3	Thermo Fisher	14203	1	7/1/2014	0.016	0.5	7	Lab-1
Lot 3	Thermo Fisher	14203	2	7/2/2014	0.06	0.5	7	Lab-1
Lot 3	Thermo Fisher	14203	3	7/7/2014	0.016	0.5	7	Lab-1
Lot 3	Thermo Fisher	14203	4	7/9/2014	0.12	0.5	7	Lab-1
Lot 3	Thermo Fisher	14203	5	7/14/2014	0.016	0.5	7	Lab-1
Lot 3	Thermo Fisher	14203	6	7/16/2014	0.016	0.5	7	Lab-1
Lot 3	Thermo Fisher	14203	7	7/17/2014	0.016	0.5	7	Lab-1
Lot 3	Thermo Fisher	14203	8	7/23/2014	0.03	0.5	7	Lab-1
Lot 3	Thermo Fisher	14203	9	7/24/2014	0.06	0.5	7	Lab-1
Lot 3	Thermo Fisher	14203	10	7/25/2014	0.03	0.5	7	Lab-1
Lot 3	Thermo Fisher	14203	11	7/29/2014	0.016	0.5	7	Lab-1
Lot 3	Thermo Fisher	14203	12	7/30/2014	0.016	0.5	7	Lab-1
Lot 1	Thermo Fisher	14181	1	8/5/2014	0.03	0.06	10	Lab-2
Lot 1	Thermo Fisher	14181	2	8/5/2014	0.03	0.06	10	Lab-2
Lot 1	Thermo Fisher	14181	3	8/5/2014	0.03	0.06	10	Lab-2
Lot 1	Thermo Fisher	14181	4	8/5/2014	0.03	0.06	10	Lab-2
Lot 1	Thermo Fisher	14181	5	8/7/2014	0.03	0.06	10	Lab-2
Lot 1	Thermo Fisher	14181	6	8/7/2014	0.03	0.12	10	Lab-2
Lot 1	Thermo Fisher	14181	7	8/7/2014	0.03	0.12	10	Lab-2
Lot 1	Thermo Fisher	14181	8	8/18/2014	0.03	0.06	10	Lab-2
Lot 1	Thermo Fisher	14181	9	8/18/2014	0.03	0.06	10	Lab-2
Lot 1	Thermo Fisher	14181	10	8/18/2014	0.03	0.06	10	Lab-2
Lot 2	Thermo Fisher	14202	1	8/5/2014	0.016	0.12	10	Lab-2
Lot 2	Thermo Fisher	14202	2	8/5/2014	0.03	0.12	10	Lab-2
Lot 2	Thermo Fisher	14202	3	8/5/2014	0.016	0.12	10	Lab-2
Lot 2	Thermo Fisher	14202	4	8/5/2014	0.03	0.12	10	Lab-2
Lot 2	Thermo Fisher	14202	5	8/7/2014	0.03	0.25	10	Lab-2

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Day Read	Lab ID
Lot 2	Thermo Fisher	14202	6	8/7/2014	0.03	0.12	10	Lab-2
Lot 2	Thermo Fisher	14202	7	8/7/2014	0.03	0.12	10	Lab-2
Lot 2	Thermo Fisher	14202	8	8/18/2014	0.03	0.12	10	Lab-2
Lot 2	Thermo Fisher	14202	9	8/18/2014	0.03	0.12	10	Lab-2
Lot 2	Thermo Fisher	14202	10	8/18/2014	0.016	0.12	10	Lab-2
Lot 3	Thermo Fisher	14203	1	8/5/2014	0.03	1	10	Lab-2
Lot 3	Thermo Fisher	14203	2	8/5/2014	0.016	0.5	10	Lab-2
Lot 3	Thermo Fisher	14203	3	8/5/2014	0.016	1	10	Lab-2
Lot 3	Thermo Fisher	14203	4	8/5/2014	0.016	1	10	Lab-2
Lot 3	Thermo Fisher	14203	5	8/7/2014	0.03	0.5	10	Lab-2
Lot 3	Thermo Fisher	14203	6	8/7/2014	0.03	0.5	10	Lab-2
Lot 3	Thermo Fisher	14203	7	8/7/2014	0.03	1	10	Lab-2
Lot 3	Thermo Fisher	14203	8	8/18/2014	0.016	0.5	10	Lab-2
Lot 3	Thermo Fisher	14203	9	8/18/2014	0.016	0.5	10	Lab-2
Lot 3	Thermo Fisher	14203	10	8/18/2014	0.03	0.5	10	Lab-2
Lot 1	Thermo Fisher	14181	1	9/2/2014	0.03	0.06	10	Lab-3
Lot 1	Thermo Fisher	14181	2	9/2/2014	0.03	0.06	10	Lab-3
Lot 1	Thermo Fisher	14181	3	9/2/2014	0.03	0.06	10	Lab-3
Lot 1	Thermo Fisher	14181	4	9/2/2014	0.03	0.06	10	Lab-3
Lot 1	Thermo Fisher	14181	5	9/2/2014	0.03	0.06	10	Lab-3
Lot 1	Thermo Fisher	14181	6	9/2/2014	0.03	0.06	10	Lab-3
Lot 1	Thermo Fisher	14181	7	9/2/2014	0.03	0.06	10	Lab-3
Lot 1	Thermo Fisher	14181	8	9/2/2014	0.03	0.06	10	Lab-3
Lot 1	Thermo Fisher	14181	9	9/2/2014	0.03	0.06	10	Lab-3
Lot 1	Thermo Fisher	14181	10	9/2/2014	0.03	0.06	10	Lab-3
Lot 2	Thermo Fisher	14202	1	9/4/2014	0.03	0.12	10	Lab-3
Lot 2	Thermo Fisher	14202	2	9/4/2014	0.016	0.12	10	Lab-3

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Day Read	Lab ID
Lot 2	Thermo Fisher	14202	3	9/4/2014	0.016	0.12	10	Lab-3
Lot 2	Thermo Fisher	14202	4	9/4/2014	0.016	0.12	10	Lab-3
Lot 2	Thermo Fisher	14202	5	9/4/2014	0.016	0.12	10	Lab-3
Lot 2	Thermo Fisher	14202	6	9/9/2014	0.03	0.12	10	Lab-3
Lot 2	Thermo Fisher	14202	7	9/9/2014	0.016	0.12	10	Lab-3
Lot 2	Thermo Fisher	14202	8	9/9/2014	0.016	0.12	10	Lab-3
Lot 2	Thermo Fisher	14202	9	9/9/2014	0.016	0.12	10	Lab-3
Lot 2	Thermo Fisher	14202	10	9/9/2014	0.016	0.12	10	Lab-3
Lot 3	Thermo Fisher	14203	1	9/4/2014	0.016	0.12	10	Lab-3
Lot 3	Thermo Fisher	14203	2	9/4/2014	0.03	0.12	10	Lab-3
Lot 3	Thermo Fisher	14203	3	9/4/2014	0.016	0.12	10	Lab-3
Lot 3	Thermo Fisher	14203	4	9/4/2014	0.016	0.12	10	Lab-3
Lot 3	Thermo Fisher	14203	5	9/4/2014	0.016	0.12	10	Lab-3
Lot 3	Thermo Fisher	14203	6	9/4/2014	0.016	0.12	10	Lab-3
Lot 3	Thermo Fisher	14203	7	9/4/2014	0.016	0.12	10	Lab-3
Lot 3	Thermo Fisher	14203	8	9/4/2014	0.016	0.12	10	Lab-3
Lot 3	Thermo Fisher	14203	9	9/4/2014	0.016	0.12	10	Lab-3
Lot 3	Thermo Fisher	14203	10	9/4/2014	0.016	0.12	10	Lab-3
Lot 1	Thermo Fisher	14181	1	8/29/2014	0.03	<0.03	10	Lab-4
Lot 1	Thermo Fisher	14181	2	8/29/2014	0.06	0.06	10	Lab-4
Lot 1	Thermo Fisher	14181	3	8/29/2014	0.03	<0.03	10	Lab-4
Lot 1	Thermo Fisher	14181	4	9/1/2014	0.03	0.06	10	Lab-4
Lot 1	Thermo Fisher	14181	5	9/1/2014	NR	NR	10	Lab-4
Lot 1	Thermo Fisher	14181	6	9/1/2014	0.06	0.06	10	Lab-4
Lot 1	Thermo Fisher	14181	7	9/5/2014	0.016	0.06	10	Lab-4
Lot 1	Thermo Fisher	14181	8	9/5/2014	0.06	<0.03	10	Lab-4
Lot 1	Thermo Fisher	14181	9	9/5/2014	0.06	0.06	10	Lab-4

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Day Read	Lab ID
Lot 1	Thermo Fisher	14181	10	9/5/2014	0.06	0.06	10	Lab-4
Lot 2	Thermo Fisher	14202	1	8/29/2014	0.03	0.06	10	Lab-4
Lot 2	Thermo Fisher	14202	2	8/29/2014	0.03	0.06	10	Lab-4
Lot 2	Thermo Fisher	14202	3	8/29/2014	0.03	0.06	10	Lab-4
Lot 2	Thermo Fisher	14202	4	9/1/2014	0.03	0.06	10	Lab-4
Lot 2	Thermo Fisher	14202	5	9/1/2014	0.016	0.06	10	Lab-4
Lot 2	Thermo Fisher	14202	6	9/1/2014	0.016	0.06	10	Lab-4
Lot 2	Thermo Fisher	14202	7	9/5/2014	0.016	0.06	10	Lab-4
Lot 2	Thermo Fisher	14202	8	9/5/2014	0.016	0.06	10	Lab-4
Lot 2	Thermo Fisher	14202	9	9/5/2014	0.03	0.06	10	Lab-4
Lot 2	Thermo Fisher	14202	10	9/5/2014	0.03	0.06	10	Lab-4
Lot 3	Thermo Fisher	14203	1	8/29/2014	0.03	0.5	10	Lab-4
Lot 3	Thermo Fisher	14203	2	8/29/2014	0.016	0.5	10	Lab-4
Lot 3	Thermo Fisher	14203	3	8/29/2014	0.03	0.5	10	Lab-4
Lot 3	Thermo Fisher	14203	4	9/1/2014	0.016	0.5	10	Lab-4
Lot 3	Thermo Fisher	14203	5	9/1/2014	0.016	0.5	10	Lab-4
Lot 3	Thermo Fisher	14203	6	9/1/2014	0.03	0.5	10	Lab-4
Lot 3	Thermo Fisher	14203	7	9/5/2014	0.016	0.5	10	Lab-4
Lot 3	Thermo Fisher	14203	8	9/5/2014	0.03	0.5	10	Lab-4
Lot 3	Thermo Fisher	14203	9	9/5/2014	0.016	0.5	10	Lab-4
Lot 3	Thermo Fisher	14203	10	9/5/2014	0.03	0.5	10	Lab-4
Lot 1	Thermo Fisher	14181	1	8/20/2014	0.03	0.06	10	Lab-5
Lot 1	Thermo Fisher	14181	2	8/20/2014	0.03	0.25	10	Lab-5
Lot 1	Thermo Fisher	14181	3	8/20/2014	0.03	0.06	10	Lab-5
Lot 1	Thermo Fisher	14181	4	8/20/2014	0.03	0.12	10	Lab-5
Lot 1	Thermo Fisher	14181	5	8/20/2014	0.03	0.12	10	Lab-5
Lot 1	Thermo Fisher	14181	6	8/20/2014	0.03	0.06	10	Lab-5

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Day Read	Lab ID
Lot 1	Thermo Fisher	14181	7	8/20/2014	0.03	0.06	10	Lab-5
Lot 1	Thermo Fisher	14181	8	8/20/2014	0.016	0.06	10	Lab-5
Lot 1	Thermo Fisher	14181	9	8/20/2014	0.03	0.06	10	Lab-5
Lot 1	Thermo Fisher	14181	10	8/20/2014	0.03	0.06	10	Lab-5
Lot 2	Thermo Fisher	14202	1	8/22/2014	0.016	0.06	10	Lab-5
Lot 2	Thermo Fisher	14202	2	8/22/2014	0.008	0.06	10	Lab-5
Lot 2	Thermo Fisher	14202	3	8/22/2014	0.016	0.06	10	Lab-5
Lot 2	Thermo Fisher	14202	4	8/22/2014	0.016	0.12	10	Lab-5
Lot 2	Thermo Fisher	14202	5	8/22/2014	0.016	0.06	10	Lab-5
Lot 2	Thermo Fisher	14202	6	8/22/2014	0.03	0.12	10	Lab-5
Lot 2	Thermo Fisher	14202	7	8/22/2014	0.016	0.12	10	Lab-5
Lot 2	Thermo Fisher	14202	8	8/22/2014	0.016	0.12	10	Lab-5
Lot 2	Thermo Fisher	14202	9	8/22/2014	0.016	0.12	10	Lab-5
Lot 2	Thermo Fisher	14202	10	8/22/2014	0.016	0.12	10	Lab-5
Lot 3	Thermo Fisher	14203	1	8/22/2014	0.016	0.5	10	Lab-5
Lot 3	Thermo Fisher	14203	2	8/22/2014	0.008	0.5	10	Lab-5
Lot 3	Thermo Fisher	14203	3	8/22/2014	0.016	0.5	10	Lab-5
Lot 3	Thermo Fisher	14203	4	8/22/2014	0.016	0.5	10	Lab-5
Lot 3	Thermo Fisher	14203	5	8/22/2014	0.016	0.5	10	Lab-5
Lot 3	Thermo Fisher	14203	6	8/22/2014	0.03	0.5	10	Lab-5
Lot 3	Thermo Fisher	14203	7	8/22/2014	0.016	0.5	10	Lab-5
Lot 3	Thermo Fisher	14203	8	8/22/2014	0.016	0.5	10	Lab-5
Lot 3	Thermo Fisher	14203	9	8/22/2014	0.016	0.5	10	Lab-5
Lot 3	Thermo Fisher	14203	10	8/22/2014	0.016	0.5	10	Lab-5
Lot 1	Thermo Fisher	14181	1	9/26/2014	0.016	0.06	10	Lab-6
Lot 1	Thermo Fisher	14181	2	9/26/2014	0.016	0.06	10	Lab-6
Lot 1	Thermo Fisher	14181	3	9/26/2014	0.016	0.06	10	Lab-6

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Day Read	Lab ID
Lot 1	Thermo Fisher	14181	4	9/26/2014	0.016	≤ 0.03	10	Lab-6
Lot 1	Thermo Fisher	14181	5	9/26/2014	0.016	0.06	10	Lab-6
Lot 1	Thermo Fisher	14181	6	9/26/2014	0.06	0.06	10	Lab-6
Lot 1	Thermo Fisher	14181	7	9/26/2014	0.016	≤ 0.03	10	Lab-6
Lot 1	Thermo Fisher	14181	8	9/26/2014	0.03	0.06	10	Lab-6
Lot 1	Thermo Fisher	14181	9	9/26/2014	0.03	0.06	10	Lab-6
Lot 1	Thermo Fisher	14181	10	9/26/2014	0.03	0.06	10	Lab-6
Lot 2	Thermo Fisher	14202	1	9/22/2014	0.03	0.06	10	Lab-6
Lot 2	Thermo Fisher	14202	2	9/22/2014	0.03	0.06	10	Lab-6
Lot 2	Thermo Fisher	14202	3	9/22/2014	0.03	0.06	10	Lab-6
Lot 2	Thermo Fisher	14202	4	9/22/2014	0.016	0.06	10	Lab-6
Lot 2	Thermo Fisher	14202	5	9/22/2014	0.03	0.06	10	Lab-6
Lot 2	Thermo Fisher	14202	6	9/22/2014	0.06	0.12	10	Lab-6
Lot 2	Thermo Fisher	14202	7	9/22/2014	0.06	0.12	10	Lab-6
Lot 2	Thermo Fisher	14202	8	9/22/2014	0.03	0.12	10	Lab-6
Lot 2	Thermo Fisher	14202	9	9/22/2014	0.06	0.06	10	Lab-6
Lot 2	Thermo Fisher	14202	10	9/22/2014	0.06	0.06	10	Lab-6
Lot 3	Thermo Fisher	14203	1	9/29/2014	0.03	0.5	10	Lab-6
Lot 3	Thermo Fisher	14203	2	9/29/2014	0.016	0.5	10	Lab-6
Lot 3	Thermo Fisher	14203	3	9/29/2014	0.03	0.5	10	Lab-6
Lot 3	Thermo Fisher	14203	4	9/29/2014	0.03	0.5	10	Lab-6
Lot 3	Thermo Fisher	14203	5	9/29/2014	0.03	0.5	10	Lab-6
Lot 3	Thermo Fisher	14203	6	9/29/2014	0.016	0.5	10	Lab-6
Lot 3	Thermo Fisher	14203	7	9/29/2014	0.016	0.5	10	Lab-6
Lot 3	Thermo Fisher	14203	8	9/29/2014	0.03	0.5	10	Lab-6
Lot 3	Thermo Fisher	14203	9	9/29/2014	0.016	0.5	10	Lab-6
Lot 3	Thermo Fisher	14203	10	9/29/2014	NR	0.5	10	Lab-6

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Day Read	Lab ID
Lot 1	Thermo Fisher	14181	1	9/29/2014	0.06	0.12	10	Lab-7
Lot 1	Thermo Fisher	14181	2	9/29/2014	0.06	0.03	10	Lab-7
Lot 1	Thermo Fisher	14181	3	9/29/2014	0.06	0.03	10	Lab-7
Lot 1	Thermo Fisher	14181	4	9/29/2014	0.06	0.06	10	Lab-7
Lot 1	Thermo Fisher	14181	5	9/29/2014	0.06	0.06	10	Lab-7
Lot 1	Thermo Fisher	14181	6	9/30/2014	0.06	0.06	10	Lab-7
Lot 1	Thermo Fisher	14181	7	9/30/2014	0.06	0.06	10	Lab-7
Lot 1	Thermo Fisher	14181	8	9/30/2014	0.06	0.06	10	Lab-7
Lot 1	Thermo Fisher	14181	9	9/30/2014	0.06	0.03	10	Lab-7
Lot 1	Thermo Fisher	14181	10	9/30/2014	0.03	0.06	10	Lab-7
Lot 2	Thermo Fisher	14202	1	9/29/2014	0.06	0.06	10	Lab-7
Lot 2	Thermo Fisher	14202	2	9/29/2014	0.06	0.12	10	Lab-7
Lot 2	Thermo Fisher	14202	3	9/29/2014	0.06	0.06	10	Lab-7
Lot 2	Thermo Fisher	14202	4	9/29/2014	0.03	0.06	10	Lab-7
Lot 2	Thermo Fisher	14202	5	9/29/2014	0.03	0.06	10	Lab-7
Lot 2	Thermo Fisher	14202	6	9/30/2014	0.06	0.06	10	Lab-7
Lot 2	Thermo Fisher	14202	7	9/30/2014	0.06	0.06	10	Lab-7
Lot 2	Thermo Fisher	14202	8	9/30/2014	0.06	0.06	10	Lab-7
Lot 2	Thermo Fisher	14202	9	9/30/2014	0.03	0.06	10	Lab-7
Lot 2	Thermo Fisher	14202	10	9/30/2014	0.03	0.06	10	Lab-7
Lot 3	Thermo Fisher	14203	1	9/29/2014	0.03	0.25	10	Lab-7
Lot 3	Thermo Fisher	14203	2	9/29/2014	0.03	0.12	10	Lab-7
Lot 3	Thermo Fisher	14203	3	9/29/2014	0.06	0.12	10	Lab-7
Lot 3	Thermo Fisher	14203	4	9/29/2014	0.03	0.25	10	Lab-7
Lot 3	Thermo Fisher	14203	5	9/29/2014	0.06	0.25	10	Lab-7
Lot 3	Thermo Fisher	14203	6	9/30/2014	0.06	0.25	10	Lab-7
Lot 3	Thermo Fisher	14203	7	9/30/2014	0.03	0.06	10	Lab-7

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Day Read	Lab ID
Lot 3	Thermo Fisher	14203	8	9/30/2014	0.06	0.12	10	Lab-7
Lot 3	Thermo Fisher	14203	9	9/30/2014	0.06	0.25	10	Lab-7
Lot 3	Thermo Fisher	14203	10	9/30/2014	0.03	0.25	10	Lab-7
Lot 1	Thermo Fisher	14181	1	8/13/2014	0.016	0.06	14	Lab-8
Lot 1	Thermo Fisher	14181	2	8/20/2014	0.03	0.06	14	Lab-8
Lot 1	Thermo Fisher	14181	3	8/27/2014	0.03	0.06	14	Lab-8
Lot 1	Thermo Fisher	14181	4	9/3/2014	0.016	0.06	14	Lab-8
Lot 1	Thermo Fisher	14181	5	9/4/2014	0.03	0.12	14	Lab-8
Lot 1	Thermo Fisher	14181	6	9/11/2014	0.03	0.06	14	Lab-8
Lot 1	Thermo Fisher	14181	7	9/15/2014	0.03	0.06	14	Lab-8
Lot 1	Thermo Fisher	14181	8	9/24/2014	0.016	0.06	14	Lab-8
Lot 1	Thermo Fisher	14181	9	10/2/2014	0.03	0.06	14	Lab-8
Lot 1	Thermo Fisher	14181	10	10/9/2014	0.03	0.06	14	Lab-8
Lot 1	Thermo Fisher	14181	11	10/12/2014	0.016	0.5	14	Lab-8
Lot 2	Thermo Fisher	14202	1	8/13/2014	0.03	0.12	14	Lab-8
Lot 2	Thermo Fisher	14202	2	8/20/2014	<0.008	0.06	14	Lab-8
Lot 2	Thermo Fisher	14202	3	8/27/2014	0.016	0.12	14	Lab-8
Lot 2	Thermo Fisher	14202	4	9/3/2014	0.016	0.12	14	Lab-8
Lot 2	Thermo Fisher	14202	5	9/4/2014	0.016	0.12	14	Lab-8
Lot 2	Thermo Fisher	14202	6	9/11/2014	0.016	0.12	14	Lab-8
Lot 2	Thermo Fisher	14202	7	9/15/2014	0.016	0.12	14	Lab-8
Lot 2	Thermo Fisher	14202	8	9/24/2014	0.016	0.12	14	Lab-8
Lot 2	Thermo Fisher	14202	9	10/2/2014	0.016	0.12	14	Lab-8
Lot 2	Thermo Fisher	14202	10	10/9/2014	0.016	0.12	14	Lab-8
Lot 2	Thermo Fisher	14202	11	10/12/2014	0.016	1	14	Lab-8
Lot 3	Thermo Fisher	14203	1	8/13/2014	0.016	0.12	14	Lab-8
Lot 3	Thermo Fisher	14203	2	8/20/2014	0.016	0.12	14	Lab-8

Media Lot No	Supplier	Supplier's Lot No	DST No	Date of DST	BDQ MIC (μg/mL)	INH MIC (μg/mL)	Day Read	Lab ID
Lot 3	Thermo Fisher	14203	3	8/27/2014	0.016	0.5	14	Lab-8
Lot 3	Thermo Fisher	14203	4	9/3/2014	0.016	0.5	14	Lab-8
Lot 3	Thermo Fisher	14203	5	9/4/2014	0.016	1	14	Lab-8
Lot 3	Thermo Fisher	14203	6	9/11/2014	0.016	1	14	Lab-8
Lot 3	Thermo Fisher	14203	7	9/15/2014	0.016	1	14	Lab-8
Lot 3	Thermo Fisher	14203	8	9/24/2014	0.03	1	14	Lab-8
Lot 3	Thermo Fisher	14203	9	10/2/2014	<0.008	1	14	Lab-8
Lot 3	Thermo Fisher	14203	10	10/9/2014	0.016	1	14	Lab-8
Lot 3	Thermo Fisher	14203	11	10/12/2014	0.03	1	14	Lab-8

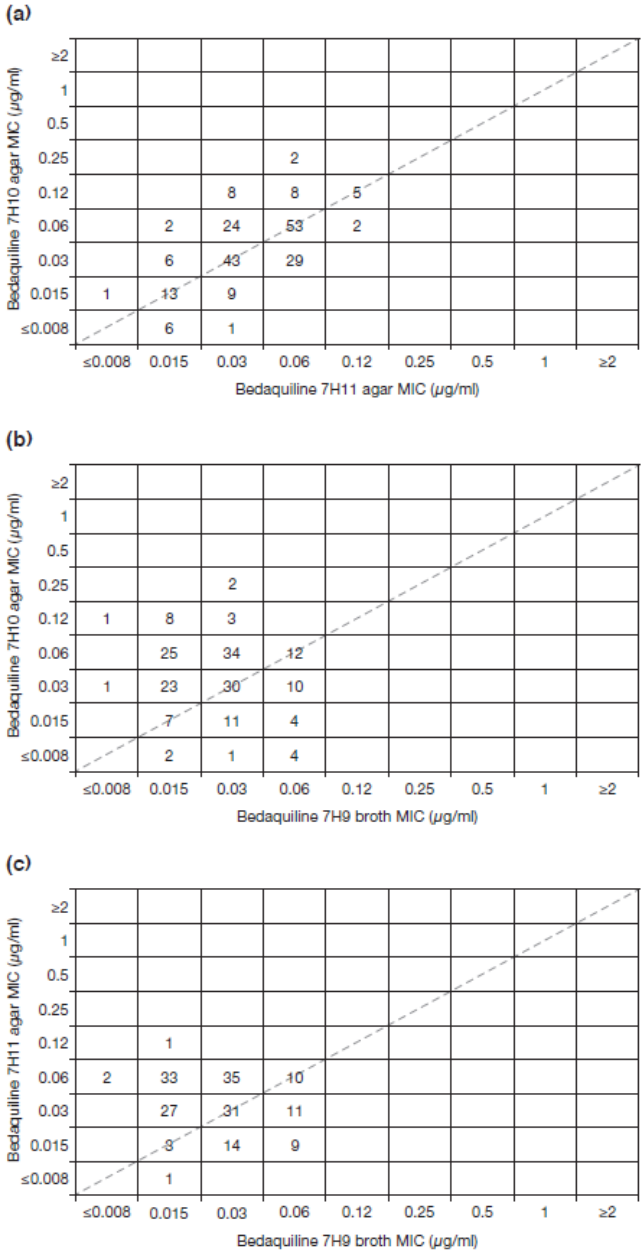

Figure S1. Comparison of bedaquiline MICs in different media against MTB H37Rv (a) 7H10 agar versus 7H11 agar dilution excluding data from Lab-5 (*n*=212). Pearson correlation coefficient (R-value) of 0.58550; *P*≤0.0001. Intermethod correlation (±1 dilution) of 93.9% essential agreement; (b) Bedaquiline 7H10 agar dilution versus 7H9 broth microdilution excluding data from Lab-5 and Lab-1 (*n*=178). Pearson correlation coefficient (R-value) of –0.15700. Intermethod correlation (±1 dilution) of 72.5% essential agreement; (c) Bedaquiline 7H11 agar dilution versus 7H9 broth microdilution excluding data from Lab-5 and Lab-1 (*n*=177). Pearson correlation coefficient (R-value) of –0.22055. Intermethod correlation (±1 dilution) of 74.6% essential agreement.