Division of TB Elimination
Reference Laboratory

Instructions for U.S. Public Health Laboratory Submission of *Mycobacterium tuberculosis* Complex Isolates for Phenotypic Drug Susceptibility Testing of Bedaquiline for the Bedaquiline Patient-Exposure Registry

Centers for Disease Control and Prevention
Division of Tuberculosis Elimination Laboratory Branch
1600 Clifton Road, NE, F08
Atlanta, Georgia 30329
e-mail: TBLab@cdc.gov
Telephone: 404-639-1285
Fax: 404-639-5491

Table of Contents

US Bedaquiline Patient-Exposure Registry (BPR)
Phenotypic Drug Susceptibility Testing (DST)

1. Introduction

SIRTURO (Bedaquiline) is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (≥ 18 years) with pulmonary multidrug-resistant tuberculosis (MDR-TB). Bedaquiline (BDQ) is indicated for use when an effective treatment regimen cannot otherwise be provided and should be administered by directly observed therapy (DOT). The use of BDQ in the following settings is not recommended due to lack of safety and efficacy data: treatment of drug-sensitive TB, treatment of latent infection due to *Mycobacterium tuberculosis*, treatment of extra-pulmonary TB (e.g., central nervous system), and the treatment of infections caused by non-tuberculous mycobacteria (NTM).

Post marketing requirements conditional upon the accelerated approval of BDQ by the United States (U.S) Food and Drug Administration (FDA) included the development of a patient registry for BDQ-treated patients. In accordance with this requirement, a primary objective of the Bedaquiline Patient-Exposure Registry (BPR) is to meet the FDA request to describe the susceptibility data based on BDQ Minimum Inhibitory Concentrations (MICs) for baseline and any subsequent follow-up isolates from MDR-TB patients treated with BDQ. The Laboratory Branch of the Division of Tuberculosis Elimination at U.S. CDC provides the BDQ DST service for BPR. This service can be incorporated as part of CDC's Molecular Detection of Drug Resistance (MDDR) service (http://www.cdc.gov/tb/topic/laboratory/mddrusersguide.pdf). The service allows rapid identification of MDR TB through the detection of genetic mutations associated with rifampin (RMP) and isoniazid (INH) resistance. In addition, when resistance to RMP is already known or detected in the MDDR service, genetic loci associated with resistance to ethambutol (EMB), pyrazinamide (PZA), and the most effective second-line drugs, fluoroquinolones (FQ) and the injectables amikacin (AMK), kanamycin (KAN), and capreomycin (CAP), are examined. In addition to molecular analysis, conventional drug susceptibility testing (DST) is performed.

For the BPR, the DST will include determination of BDQ MIC by both 7H10 agar and 7H9 broth methods on baseline and post-baseline isolates. Only the MIC determined by the 7H9 broth method will be reported in real-time. All 7H10 agar testing and testing of post-baseline isolates will be performed in batch. Currently, there is not a validated molecular assay for detecting resistance to BDQ.

2. Overview of the Process

Healthcare providers (HCPs) collect sputa from patients at first and subsequent follow-up visits and submit to their local laboratory for TB testing (e.g., AFB smear and culture, Xpert MTB/RIF or other direct detection assay) and if *Mycobacterium tuberculosis* complex (MTBC) is present, isolates are submitted, most often to a state public health laboratory for DST. Isolates for BDQ DST are submitted to CDC through the public health laboratory and test results are reported back to the submitting laboratory who, in turn, reports to the primary HCP.

3. Submission Criteria for DST in BPR

- Initial and follow-up (i.e., monthly) isolates of MTBC and processed sputum sediments that are nucleic acid amplification test positive (NAAT+) may be submitted by U.S. public health laboratories for BDQ DST if they originated from MDR-TB patients.
- Standard of care testing (i.e., smear, culture, and DST) should be performed in the submitting laboratory when NAAT+ sputum sediments are submitted for MDDR/BDQ DST.

4. Sample Types Accepted By CDC

NAAT+ sputum sediments and initial and follow-up (i.e., monthly) isolates of MTBC will be accepted. Isolates can be submitted on solid media slants (LJ or Middlebrook) or as positive MGIT, BacT/ALERT, or VersaTREK cultures. Alternatively, laboratories may choose to submit a portion of the growth from solid media in a cryovial (e.g., the growth can be scraped off the slant or plate and placed in the vial, preferable with a small piece of the media). When shipping liquid culture, a MGIT tube is acceptable. Otherwise, please send 1 ml of culture in a screw-cap cryovial (with external threads on tube) that has been sealed with parafilm. Similarly, when shipping sputum sediments, please send 0.5–1 ml in a screw-cap cryovial (with external threads on tube) that has

been sealed with parafilm. Do not send any samples in 50 ml conical tubes. Slants or vials must be clearly labeled with at least the number entered into the Specimen ID field on the CDC Specimen Submission Form (http://www.cdc.gov/laboratory/specimen-submission/pdf/form-50-34.pdf).

5. How do I Submit a Sample for the BDQ DST Service?

State Public Health Laboratories will complete appropriate portions of the **CDC Specimen Submission Form -50-34** (http://www.cdc.gov/laboratory/specimen-submission/pdf/form-50-34.pdf)**.** BDQ DST must be specifically requested to alert the CDC that the submission is for the BPR.

In LABORATORY EXAMINATION REQUESTED box on the form enter the following:

:

Test order name: Mycobacterium TB Complex – Special Study

Test order code: CDC-10191

Suspected agent: MTBC

Date sent to CDC: MM/DD/YYYY

At CDC, bring to the attention of: **BDQ Patient-Exposure Registry**

Isolates should be **shipped via overnight service to CDC Monday through Thursday. Do not ship on Friday.** Liquid samples do not need to be shipped on dry ice. Samples should be shipped in compliance with federal regulation.

http://www.cdc.gov/ncidod/srp/specimens/shipping-packing.html (shipping information)

Shipping address:

Bedaquiline Patient-Exposure Registry
ATTN: Beverly Metchock, Unit 29
1600 Clifton Road, NE, F08
Atlanta, GA. 30329
Tel: 404-639-1285

Janssen has established an Account with World Courier for shipment free of charge to the submitter: To place an order, please call 24/7/365 World Courier customer service 1 800 221 6600 (www.worldcourier.com) and provide Account 20324.

Question regarding shipment should be addressed to:

Mike Gordon

World Courier

Email: mgordon@worldcourier.com

Tel: 1 800 221 6600 Ext 3339

Mobile: 631 839-3834

6. Protocol for 7H10 Agar and 7H9 Broth DST

Study protocols supplied by Jannsen will be used for 7H10 agar and 7H9 broth DST.

7. How Will BPR DST Results Be Reported?

For baseline isolates, reports will be issued by FAX or secure e-mail to the submitting laboratory as soon as results are available. For isolates tested in batch (i.e., post-baseline isolates, 7H10 agar DST), results will be reported by FAX or secure e-mail when all testing is completed. The submitting laboratory is responsible for dissemination of CDC reports to the TB program/clinician (HCP) as appropriate. The HCP is responsible for reporting the DST results in the BPR.

8. What If I Have Trouble Interpreting DST Results?

Laboratorians, TB control personnel, and clinicians can contact the CDC for help in interpretation of reports.

e-mail: TBLab@cdc.gov

Telephone: 404-639-1285