Guidance for Industry

Pulmonary Tuberculosis: Developing Drugs for Treatment

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2013
Clinical Antimicrobial

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of pulmonary tuberculosis.[2] Specifically, this guidance addresses the FDA's current thinking regarding the overall development program and clinical trial designs for drugs to support an indication for the treatment of active pulmonary tuberculosis. This draft guidance is intended to serve as a focus for continued discussions among the Division of Anti-Infective Products, pharmaceutical sponsors, the academic community, and the public.[3]

This guidance applies to the development of a single investigational drug as well as to the development of two or more new investigational drugs for use in combination. Sponsors interested in development of two or more new investigational drugs for use in combination should refer to the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination*[4] and discuss the overall development plans with the FDA.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical*

[1] This guidance has been prepared by the Division of Anti-Infective Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during clinical development.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

Principles for Clinical Trials and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Tuberculosis infections caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) remain endemic in the United States and epidemic in many parts of the world. Resistance to multiple drugs and the emergence of the human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) epidemic created new challenges in the management of tuberculosis. Drugs with new mechanisms of action, improved safety profiles, fewer drug-drug interactions (especially for patients needing concurrent treatment of HIV/AIDS), and use of shorter-course combination regimens are needed to manage tuberculosis. The FDA has convened a number of public discussions on the issues related to clinical trial designs for tuberculosis.[5]

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

The activity of investigational antimycobacterial drugs can be evaluated in trials of early bactericidal activity and/or in phase 2 trials that evaluate microbiologic outcomes at early time points.

a. Early bactericidal activity

Early bactericidal activity (EBA) trials evaluating the quantitative counts of viable tubercle bacilli from daily collections of sputum can provide information on the bactericidal activity of single drugs or a new regimen in clearing *M. tuberculosis* from the sputum of patients with newly diagnosed pulmonary tuberculosis. These trials are not intended to provide definitive treatment for patients but rather to evaluate antimycobacterial activity in a brief setting (7 to 14 days). The value of an EBA trial includes the preliminary evaluations of antimycobacterial

[5] Meeting information and transcripts from Anti-Infective Drugs Advisory Committee meetings held on June 3, 2009 (general discussion of trial designs), and November 28, 2012 (discussion of the review of a specific new drug application), can be found at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm125599.htm and http://www.fda.gov/AdvisoryCommittees/Calendar/ucm321011.htm, respectively; the 2009 FDA pulmonary tuberculosis workshop transcripts can be found at http://www.fda.gov/Drugs/NewsEvents/ucm168975.htm.

activity of a new drug or regimen over the course of 7 to 14 days. Patients appropriate for enrollment in EBA trials would be immunocompetent, treatment-naïve adults at low risk of drug resistance or extrapulmonary disease, who can begin standard-of-care treatment for pulmonary tuberculosis at the completion of the EBA trial.

b. Phase 2 evaluations

Phase 2 trials designed to assess antimycobacterial activity (e.g., an 8-week evaluation of the absence of acid fast bacilli (AFB) in sputum) of the investigational drug(s) when combined with other antimycobacterial drugs as part of a treatment regimen can be useful for evaluating possible doses or regimens before initiating phase 3 trials.

2. Drug Development Populations

The trial populations should include adults with pulmonary tuberculosis. The presence of extrapulmonary disease may require longer durations of therapy than pulmonary tuberculosis and assessment of endpoints that evaluate the extrapulmonary site. When trials include patients with pulmonary tuberculosis and concurrent extrapulmonary involvement, the pharmacokinetics, including elimination pathways and tissue distribution characteristics, of the investigational drug should be well characterized (i.e., genitourinary tuberculosis may be amenable to therapy with drugs primarily excreted by renal metabolism). Trials can include patients with drug-resistant pulmonary tuberculosis who are able to be treated with effective antimycobacterial drug regimens. In patients with extensively drug-resistant tuberculosis (CDC 2006), for whom there are limited or no available effective antimycobacterial drugs, the evaluation of two or more new investigational drugs should be considered.[6]

3. Efficacy Considerations

Trials of investigational drugs for the treatment of tuberculosis can be designed to show that a new drug as part of a treatment regimen (or as an entirely new regimen) is effective based on a superiority test or noninferiority test. A single adequate and well-controlled trial in patients with pulmonary tuberculosis, supported by other independent evidence (e.g., evidence of antimycobacterial activity from an EBA trial), can provide evidence of effectiveness when the single trial has demonstrated a clinically meaningful treatment effect.[7]

4. Safety Considerations

The evaluation of the safety profile of an investigational antimycobacterial drug can be challenging because patients with pulmonary tuberculosis often have comorbid conditions. In addition, the co-administration with other antimycobacterial drugs (potentially including other investigational antimycobacterial drugs) or other concomitant medications provides additional challenges to the safety evaluation of an investigational drug for treatment of pulmonary

[6] See the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination*.

[7] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

tuberculosis. If severe adverse effects occur in a patient enrolled in a clinical trial, it is generally recommended that all drugs for treatment of tuberculosis, including the investigational drug(s), be stopped simultaneously and restarted one at a time to explore which drug may be causing the adverse effect (CDC 2003).

Treatment guidelines from the American Thoracic Society, Centers for Disease Control and Prevention, and the Infectious Diseases Society of America provide recommendations for the management of patients with adverse effects caused by one or more drugs used in a treatment regimen. For example, the guidelines suggest that standard therapy for pulmonary tuberculosis should be stopped in the setting of acute hepatitis, which could be drug-induced hepatitis caused by isoniazid, pyrazinamide, or rifampin. Two or more antimycobacterial drugs without known hepatotoxicity can be used for treatment until the cause for hepatitis has been identified. After symptom improvement and liver function test normalization, standard therapy (e.g., rifampin, isoniazid, pyrazinamide, ethambutol) can be restarted in a sequential fashion with close monitoring of liver function tests (CDC 2003).

In general, sponsors should discuss with the FDA the size of the needed preapproval safety database during drug development. An appropriate preapproval safety database is approximately 500 or more patients treated at the dose and duration of therapy recommended in labeling. For assessment of risks and benefits in patients with drug-resistant tuberculosis, an unmet medical need, a preapproval safety database of approximately 300 patients may be sufficient.

In trials that include two or more investigational drugs in one treatment arm, if an unexpected adverse effect occurs in the investigational treatment arm, it may be difficult to determine which of the investigational drugs is responsible for the effect. If serious adverse effects occur in clinical trials of a combination regimen, further evaluation of the role of the components of the regimen in the adverse effect is important. Data from trials that evaluate each investigational drug, if feasible, may provide important information about the adverse effects observed in trials of the combination regimen.

B. Specific Efficacy Trial Considerations

1. Trial Designs

The following trial designs can be used to demonstrate superiority:

- All patients receive an optimal background antimycobacterial treatment, one predicted to be active based on epidemiologic information and in vitro susceptibility testing when available, with randomization to add the investigational drug or matching placebo. Efficacy can be demonstrated by showing superiority of the investigational drug plus the optimized background regimen to the placebo plus the optimized background regimen.

- A regimen of one or more investigational drugs is compared to a standard regimen, with efficacy demonstrated by showing superiority of the investigational regimen over the standard regimen.[8]

[8] See the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination*.

The following trial designs can be used to demonstrate noninferiority:

- The investigational drug replaces one of the drugs of a standard multiple drug regimen. The investigational drug treatment group is within an acceptable noninferiority margin based on the known quantitative and reliable contribution within the standard regimen of the drug that has been replaced.

- An investigational drug or regimen administered for a time period of fewer than 6 months is compared to the standard regimen administered for 6 months. Noninferiority would be demonstrated by showing that the treatment-shortening regimen containing the investigational drug(s) performs within a prespecified margin of the performance of the 6-month regimen. The margin is based upon the known decrement in the performance of the 6-month standard regimen when it is administered for a shorter time period.

In an attempt to identify appropriate noninferiority margins, we reviewed data from previously conducted trials for historical evidence of sensitivity to drug effects (HESDE).[9] Based on the review, a justification for a noninferiority margin for a treatment-shortening regimen is included in the Appendix.

There may be other designs or variations of the above designs that may be suitable for evaluating the safety and efficacy of an investigational drug for the treatment of pulmonary tuberculosis. We recognize that developing informative trial designs for the study of an investigational drug in the treatment of tuberculosis presents significant challenges. Sponsors who are planning clinical trials of investigational drugs for the treatment of tuberculosis are encouraged to meet with the FDA to discuss development plans for phase 3 clinical trials.

2. Trial Population

Although a specific trial may target patients more likely to have either drug-susceptible or drug-resistant pulmonary tuberculosis, patients are likely to be randomized and enrolled before in vitro susceptibility test results are available. Protocols should specify how patients will be handled after in vitro susceptibility results are available, both in the conduct of the trial and in the analysis of the results.

Enrichment strategies for trials in drug-resistant tuberculosis can include focusing on contacts of drug-resistant tuberculosis cases, patients from areas with highly prevalent drug resistance, patients relapsing after previous treatment, and patients with disease progression on a standard drug regimen.

[9] See ICH E10 for a discussion of HESDE.

3. Inclusion and Exclusion Criteria

Recommended inclusion criteria for patients with pulmonary tuberculosis are as follows:

- Presence of AFB in a sputum specimen by smear microscopy or other rapid diagnostic test; microbiological diagnosis of tuberculosis should be confirmed by culture from at least one sputum sample obtained at the time of enrollment

- Chest radiographic findings consistent with active pulmonary tuberculosis; for example, one or more of the following findings by standardized interpretative criteria:

  - Cavitary lesion(s)
  - Apical infiltrates
  - Hilar lymphadenopathy
  - New infiltrate

- A minimum of two signs or symptoms that have been present for at least 2 weeks:

  - Sputum production
  - Cough
  - One or more episodes of hemoptysis
  - Fever (e.g., oral temperature greater than or equal to 38.0 degrees Celsius on at least two occasions)
  - Pleuritic chest pain
  - Weight loss
  - Night sweats

Use of rapid diagnostic tests may help to enroll a patient population with pulmonary tuberculosis and may help to determine drug-susceptibility and identify possible drug-resistance. The clinical trial can provide an opportunity to contribute to the development and evaluation of a new diagnostic test. Sponsors interested in the evaluation of a diagnostic test in the context of new drug or regimen development are encouraged to discuss development with the FDA and to contact the appropriate review division in the Center for Devices and Radiological Health.

Recommended exclusion criteria are as follows:

- Patients who have received 2 or more weeks of therapy for the current episode of active tuberculosis (unless being enrolled in a trial targeting drug-resistant tuberculosis and there is documented lack of response to therapy based on clinical and microbiological findings)

- Patients with significant concurrent illness that may affect outcome assessment

- Patients who are not willing to comply with recommendations from local public health authorities for the management of patients with pulmonary tuberculosis

4. Randomization, Stratification, and Blinding

Trials should be randomized and double-blinded unless a sponsor can provide a scientifically adequate explanation why blinding cannot be accomplished. If trials are single-blind or open-label, sponsors should discuss potential biases with the FDA and how these biases will be addressed.

Sponsors should consider stratification of patients at randomization by HIV status (e.g., by cluster of differentiation antigen 4 (CD4) cell counts above or below 200 cells/mm^3) and the presence or absence of cavitary disease. In trials that enroll patients with drug-resistant tuberculosis based on results of in vitro susceptibility testing, stratification can be used to address differences in the number of drugs to which patient isolates are resistant. A discussion of how the analyses will account for the stratified randomization should be included in the protocol.

If the protocol provides for enrollment of patients with concurrent disease outside the pulmonary system (extrapulmonary tuberculosis), patients with extrapulmonary disease should be either stratified at entry or analyzed separately as appropriate.

5. Specific Populations

a. Pediatric populations

Sponsors should discuss drug development in the pediatric population by the end-of-phase 2 meeting.[10] Pulmonary tuberculosis in pediatric patients can have different clinical and pathophysiologic characteristics.[11] An extrapolation of adult efficacy to pediatric populations for the treatment of pulmonary tuberculosis may be appropriate for certain pediatric populations, and sponsors should provide pharmacokinetic (PK) and safety information in a sufficient number of pediatric patients to support the appropriate dose for treatment of children with pulmonary tuberculosis.

For treatment of children who have extrapulmonary tuberculosis in which extrapolation from adult trials may not be feasible (e.g., in children under the age of 5 years with extrapulmonary tuberculosis), sponsors should provide adequate efficacy and safety in a sufficient number of pediatric patients for treatment of extrapulmonary tuberculosis, which may require a different

[10] See the Pediatric Research Equity Act (Public Law 108-155; section 505B of the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. 355B) as amended by the Food and Drug Administration Safety and Innovation Act of 2012 (Public Law 112-114). Also see the ICH guidance for industry *E11 Clinical Investigation of Medicinal Products in the Pediatric Population*.

[11] For an example, see Perez-Velez and Marais 2012.

dose and duration of therapy in comparison to treatment of pulmonary tuberculosis. The additional safeguards of 21 CFR part 50, subpart D, for enrolling children in clinical investigations affect the timing and design of trials that support pediatric drug development. In accordance with these requirements, in general, pediatric patients can be enrolled in trials if sufficient safety and antimycobacterial activity data in adults are available and appropriate dosing regimens have been characterized.

b. Pregnant women

Tuberculosis is common among females of reproductive potential in endemic areas, and drugs being developed for tuberculosis should address use during pregnancy. When deciding whether to enroll pregnant women in clinical trials of investigational drugs to treat tuberculosis, sponsors should consider the following factors:

- Fetal risk considerations based on results from nonclinical toxicology studies, reproductive toxicology studies, and any available clinical data
- Available data about correct dosing in pregnant women
- Whether safety and efficacy have been demonstrated in nonpregnant populations
- Therapeutic options for the treatment of the pregnant patients with tuberculosis
- Ethical considerations for enrolling pregnant women in tuberculosis drug clinical trials based on maternal/fetal risk and benefit.

In situations when safe and effective treatments for tuberculosis are available for pregnant women, it is generally more appropriate to complete phase 3 clinical trials of the investigational drug(s) to establish safety and efficacy in nonpregnant patients before trials in pregnant patients are initiated.

Women with tuberculosis who become pregnant while enrolled in a clinical trial for an investigational drug could be re-consented to remain in the clinical trial if the potential benefits of continued treatment outweigh the risks of ongoing fetal exposure to the investigational drug, the risks of discontinuing maternal therapy, and/or the risks of exposing the fetus to additional drugs if the woman is placed on an alternative therapy. Such patients can provide information to evaluate correct dosing during pregnancy. Data to be collected when pregnant women are included in a clinical trial include the following elements: (1) steady-state PK assessments; (2) gestational age at enrollment; (3) gestational timing and duration of drug exposure; and (4) pregnancy outcomes including adverse maternal, fetal, and neonatal events. Infants born to mothers who received the investigational drug(s) should be followed by investigators until at least 12 months of age.[12]

[12] See the American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America guidelines for treatment of tuberculosis for recommendations regarding treatment of women during pregnancy or breast-feeding (CDC 2003).

c. Other specific populations

Geriatric patients,[13] patients with renal insufficiency, and patients with hepatic impairment should be included in trials during drug development, if feasible. Because of the high incidence of tuberculosis in patients co-infected with HIV, patients with HIV should be included in trials during drug development.

6. Dose Selection

When selecting a dosing regimen to be evaluated in phase 3 clinical trials, sponsors should consider target PK/pharmacodynamic (PD) parameters (e.g., area under the curve/minimum inhibitory concentration (MIC), maximal concentration/MIC, time above the MIC) based on in vitro models and animal models, results from early clinical trials (e.g., EBA and/or trials of clearing AFB from sputum at early time points), and results from exposure-response relationships. PK/PD evaluations based on free drug concentrations also can be an important consideration in dose selection.

7. Choice of Comparators

The choice of comparator or background regimen depends in part upon the clinical trial design (whether the trial is intended to show superiority or noninferiority) and the patient population that will be enrolled (e.g., the likelihood of infection with drug-susceptible or drug-resistant strains of *M. tuberculosis*). In general, comparator regimens should be chosen that contain FDA-approved drugs and represent standard of care. For trials of predominantly drug-resistant tuberculosis where the goal of the trial is to demonstrate superiority, the comparator arm should represent an optimized background regimen based on epidemiologic information of susceptibility and/or results from susceptibility testing. The use of comparator regimens based on local practice outside of the United States or the use of drugs that are not FDA-approved should be discussed with the FDA in advance of trial initiation.

8. Efficacy Endpoints

The following efficacy endpoints can be used in clinical trials of pulmonary tuberculosis.

- **A surrogate endpoint of no growth of *M. tuberculosis* on sputum cultures during treatment.** Demonstration of treatment effect on the rate of sputum culture conversion from positive to no growth of *M. tuberculosis* during treatment, either as a time-to-conversion analysis or at a fixed time point (e.g., at 2 months), could be considered as reasonably likely to predict clinical benefit and might support approval of a drug that provides meaningful therapeutic benefit to patients over existing treatments under the accelerated approval regulations (21 CFR 314.510 or 21 CFR 601.41). Serial cultures should be obtained at specific time points during treatment (e.g., every 2 weeks or every month). The time to sputum culture conversion is the time to the first no growth of *M. tuberculosis*, verified by no growth on at least 2 subsequent consecutive sputum cultures

[13] See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* and *E7 Studies in Support of Special Populations: Geriatrics; Questions and Answers*.

taken at least 28 days apart. Sputum cultures can be evaluated on either solid or liquid media.

- **A primary clinical efficacy endpoint that is comprised of survival and evaluation of *M. tuberculosis* on serial sputum culture examinations during treatment and 12 months following completion of treatment.**

  Clinical success is defined as patients who are alive, achieved no growth of *M. tuberculosis* on serial sputum culture examinations, did not experience relapse or recurrence of pulmonary tuberculosis, and otherwise did not meet a definition of clinical failure.

  Clinical failure is defined as having one or more of the following:

  – Protocol-defined clinical progression of pulmonary disease during treatment or unanticipated surgical intervention

  – Any growth of *M. tuberculosis* from an extrapulmonary site during the trial (unless patients with extrapulmonary tuberculosis are included at baseline)

  – Signs or symptoms of active tuberculosis, including radiographic worsening compared to baseline findings, resulting in reinitiation of antimycobacterial therapy during follow-up[14]

  – Death during treatment or follow-up

  – A sputum culture with growth of *M. tuberculosis* at certain time points outlined as follows (relapse or recurrence):

    - After a specific time point defined in the trial (in general this is expected to be any time after 2 consecutive no growth sputum cultures, taken at least 28 days apart)[15]

    - Failure to achieve no growth of *M. tuberculosis* on serial sputum cultures that result in a change in antimycobacterial therapy

- **Other endpoint considerations.** Most patients with pulmonary tuberculosis report improvement or resolution of their symptoms at therapy completion (Bark, Dietze, et al. 2011; Wejse, Gustafson, et al. 2008). However, symptom evaluations in certain patient populations may be more difficult to interpret, for example, among patients co-infected

[14] In some circumstances there may be reinitiation of antimycobacterial therapy while there is diagnostic uncertainty whether relapse has occurred, but therapy is subsequently stopped when an alternative diagnosis is established. Protocols should define the duration of retreatment therapy that will be used to define clinical failure to avoid labeling all patients in this situation as failures.

[15] Molecular evaluations of the baseline isolate and the isolate obtained at the timing of a clinical failure may help to distinguish between relapse and reinfection.

with HIV (Rangaka, Wilkinson, et al. 2012). Nevertheless, a well-defined and reliable evaluation of symptoms could be helpful in the ascertainment of treatment success if sputum specimens are not available from patients during the period of observation following therapy completion. Outcome assessment of symptoms could be based on a patient-reported outcome instrument.[16]

9. Trial Procedures and Timing of Assessments

a. Entry visit

Baseline demographic information, current medications, and complete physical examination should be obtained at this visit. In addition, the following should be included at entry:

- Clinical signs and symptoms of pulmonary tuberculosis (e.g., cough, sputum production, episodes of hemoptysis, fever, pleuritic chest pain, weight loss, night sweats).

- Baseline laboratory evaluations that include the following: (1) complete blood cell counts; (2) liver chemistry and function tests (e.g., serum albumin, alkaline phosphatase, serum aminotransferases, bilirubin, lactate dehydrogenase, prothrombin time); and (3) renal function tests (e.g., serum creatinine, blood urea nitrogen) and urinalysis.

- Additional baseline evaluations that include one or more of the following, based on the characteristics of the investigational drug and the patient population: (1) other serum chemistries (e.g., serum glucose, uric acid, phosphorous, potassium, amylase); (2) HIV serology and CD4 cell count (if HIV positive); (3) pregnancy test (in women of childbearing potential); (4) 12-lead electrocardiogram; and (5) response to tuberculin skin testing or interferon gamma release assays.

- Imaging results (standard posterior to anterior view and lateral chest radiographs, or computed tomography scans) to assess the extent and severity of pulmonary disease. Radiographic findings using standard interpretive criteria might be an important stratification criterion (e.g., the presence of cavitary lesions).

- Sputum specimens for AFB smears and mycobacterial culture obtained by one of the following: spontaneous expectoration, induction with hypertonic saline, bronchoscopy, or gastric lavage (e.g., for children). When applicable, baseline quantitative cultures should be collected in a standardized manner (e.g., single early morning induced sputum or pooled 24-hour sputum).

b. Visits during therapy and after therapy completion

As a general rule, clinical assessments should occur weekly or biweekly during the first several months of therapy, followed by monthly assessments until therapy completion. After completion

[16] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

of trial drug therapy, assessments should occur approximately every 3 months for a total of 12 months. Assessments of signs and symptoms, adverse effects, and laboratory tests, as appropriate, should occur at these visits. In addition, targeted physical examinations should be performed.

During therapy, sputum specimens for AFB smears and mycobacterial culture should be obtained at least monthly, in general. Depending on the investigational drug regimen and design, a shorter interval between specimen collections (e.g., 2 weeks) may be appropriate for certain periods of the trial.

During follow-up after therapy completion, if patients are not able to expectorate sputum spontaneously at these visits, sponsors should consider other methods to obtain sputum (e.g., induced sputum specimen).

10. Statistical Considerations

In general, a detailed statistical analysis plan stating the trial hypotheses and the analysis methods should be included in the protocol.

The primary efficacy analysis is based on the difference in proportions of patients achieving a clinical success at 12 months following therapy completion (see section III.B.8., Efficacy Endpoints, for the definition of clinical success).

A surrogate endpoint analysis can be based on no growth of *M. tuberculosis* on sputum cultures during treatment and generally would be either: (1) time-to-no-growth of *M. tuberculosis* on sputum cultures during treatment; or (2) the proportion with no growth of *M. tuberculosis* on sputum culture at a prespecified time point during treatment.

As mentioned in section III.B.8., Efficacy Endpoints, other endpoints can be considered and should be discussed with the FDA during protocol development.

Sponsors should consider the following definitions of analysis populations for a tuberculosis trial:

- Safety population: All patients who received at least one dose of investigational drug during the trial.

- Intent-to-treat (ITT): All randomized patients.

- Microbiological intent-to-treat (micro-ITT): All randomized patients with a positive culture for *M. tuberculosis* from a pretreatment sample. For trials intended to focus on patients with drug-resistant tuberculosis, sponsors can choose for the primary analysis a micro-ITT population of all randomized patients with a positive culture for a drug-resistant isolate of *M. tuberculosis* in the pretreatment sample.

- Per-protocol: All randomized patients with a positive culture from a pretreatment sample and achieving a prespecified level of compliance with the protocol (e.g., presence at follow-up visits).

In general, the analysis population of greatest interest in the determination of efficacy is the micro-ITT analysis population. In addition, consistency of the results for efficacy should be evaluated in the ITT and per-protocol populations. If there are notable differences between outcomes for the ITT and per-protocol populations, reasons for these differences should be investigated.

All patients should be followed completely for the duration of the trial even if they discontinue the investigational drug. A challenge to patients and investigators is adherence to the protocol during therapy and throughout the 12 months following therapy completion. Investigators should make every effort to minimize the loss to follow-up throughout the trial. The informed consent should emphasize the importance of continued participation for the full duration of the trial and the protocol should specify how patients will be contacted if they fail to attend a trial visit. Given that missing data is nonetheless likely to occur, the protocol should state how missing data will be handled in the primary efficacy analysis. Imbalances across treatment arms in the rate or reason for missing data will be a cause for concern and should be thoroughly discussed in the final report.

11. Accelerated Approval Considerations

Approval under 21 CFR part 314, subpart H, or 21 CFR part 601, subpart E, may be applicable to drugs developed for the treatment of tuberculosis that provide meaningful therapeutic benefit to patients over existing treatments. An endpoint based on conversion of sequential sputum cultures to no growth of *M. tuberculosis* can be used as a surrogate endpoint. Sponsors can provide scientific data to support the use of other surrogate endpoints that are reasonably likely to predict clinical benefit. When a drug is approved under accelerated approval, sponsors are required to "study the drug further, to verify and describe its clinical benefit" (21 CFR 314.510 for drugs; 21 CFR 601.41 for biologics).

12. Risk-Benefit Considerations

Because of the high rate of morbidity and mortality for patients with drug-resistant tuberculosis, caused in part by limited treatment options and epidemiological characteristics, an investigational drug's safety profile might support further development in patients with drug-resistant tuberculosis, but not drug-susceptible tuberculosis (e.g., because of an adverse effect that would not be acceptable for patients with drug-susceptible tuberculosis who have alternative therapies readily available).

C. Other Considerations

1. Clinical Microbiology Considerations

Investigational drugs being evaluated for the treatment of tuberculosis should have supportive data from in vitro microbiology and in vivo animal model studies. The mechanism of action of the drug should be identified to support its use as part of a specific treatment regimen. In vitro studies also can provide information to inform selection of the regimen of antimycobacterial drugs to be used in the investigational drug(s) clinical trials.

a. In vitro studies

In vitro studies should incorporate the following considerations:

- Studies of drug activity against metabolically active, dormant, and intracellular stages of *M. tuberculosis* are recommended. Testing against metabolically active bacilli should be performed on drug-susceptible laboratory isolates, laboratory isolates with known patterns of resistance, and isolates representing different geographical regions. These studies should identify the optimal in vitro concentration effective for inhibiting growth and/or killing the organism during metabolically active and dormant stages. The criteria for characterizing isolates as drug-susceptible or drug-resistant to the investigational drug, including the basis for establishing a critical drug concentration, should be specified.

- In vitro studies should use standardized methods for susceptibility testing such as those recommended by Clinical Laboratory Standard Institute (CLSI) Document Susceptibility Testing of Mycobacteria, Nocardiae, and other Aerobic Actinomycetes; M24-A2, or by Antimicrobial Susceptibility Test systems approved by the FDA.[17] If nonstandard methods are being employed, a complete description of the methods and the performance characteristics of the assay in the actual laboratory where testing will be done should be submitted to the FDA for review before use in the trial. Quality control parameters for in vitro susceptibility testing should be developed during phase 1 and phase 2 evaluations, and provisional interpretive criteria should be proposed before phase 3 testing. If interpretive criteria are established for labeling purposes, then testing of at least 150 clinical isolates, preferably from representative geographic areas, should be included in the analyses that support the interpretive criteria.

- In vitro models can provide an estimate for the effective dosing of an investigational drug or combination of investigational drugs to identify their potential as promising therapies for further development in treatment of pulmonary tuberculosis (e.g., PD modeling).

[17] See, for example, CLSI, 2011, Susceptibility Testing of Mycobacteria, Nocardiae, and other Aerobic Actinomycetes; Approved Standard – Second Edition, CLSI document M24-A2, CLSI 940 West Valley Rd. Suite 1400, Wayne, PA 19087-1898; and the guidance for industry *Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems* (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080564.htm).

- In vitro testing should include a study of multiple-drug regimens that contain the investigational drug(s). If two new investigational drugs are under evaluation simultaneously, factorial designs evaluating the new drugs should be carried out.

b. In vivo animal models

Appropriate animal models can serve as an important bridge between the identification of in vitro antimycobacterial effects of an investigational drug and the initiation of human clinical trials. PK assessments, toxicology findings, and changes in drug susceptibility in animal model studies may inform clinical trial designs. Evaluations of the investigational drug, or combination of investigational drugs, using different animal models or more than one isolate of *M. tuberculosis* should be considered for studying activity against different aspects of tuberculosis infection. Although animal studies are of great value, they cannot substitute for clinical trials in patients with tuberculosis to evaluate drug safety and efficacy because clinical trials can be conducted in patients with tuberculosis.[18]

c. Drug resistance and cross-resistance

The potential of *M. tuberculosis* isolates to develop resistance to the investigational drug should be examined in appropriate in vitro and/or in vivo models and should include evaluating the potential for cross-resistance to drugs in the same class or in other classes. If resistance is demonstrated, it is important to identify the mechanism of resistance. Attempts should be made to evaluate the clinical significance of any changes in phenotype (e.g., in vitro susceptibility to the drug) or genotype observed in nonclinical studies by correlating such changes with outcomes.

d. Types of culture media to identify *M. tuberculosis*

Solid media (e.g., Löwenstein-Jensen media) and liquid media (e.g., mycobacteria growth indicator tube) are culture assay methods available to identify and characterize *M. tuberculosis*. Either solid media or liquid media, or both, can be used in clinical development. The type of culture media has implications for the trial. For example, mycobacterial growth can take less than 2 weeks in liquid media, while growth on solid media can take up to 6 weeks. Also, there are newer molecular methodologies to detect *M. tuberculosis* and its susceptibility profile that can be included in the trial's microbiology considerations. Sponsors should specify in the clinical trial protocol the methods to culture and identify *M. tuberculosis* as well as the in vitro susceptibility testing methods that will be employed. The following are microbiological approaches for identification and characterization of *M. tuberculosis.*

- **Using solid and liquid media for the baseline culture.** The sputum specimen is evaluated simultaneously on both solid and liquid media. The advantages to this approach are: (1) a more rapid observation of mycobacterial growth in liquid media (e.g., less than 2 weeks); (2) growth of pure culture on solid media is already underway for the biochemical confirmation of *M. tuberculosis*; and (3) growth of pure culture on solid media is already underway for the evaluation of in vitro susceptibility tests.

[18] See 21 CFR 314.600, subpart I, Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible.

- **Using liquid media for the baseline culture**

  – The sputum specimen is evaluated in liquid media. The advantage is a more rapid observation of mycobacterial growth. The disadvantage is a potential delay in the identification and characterization of the liquid culture isolate, because the isolate would then need to be subcultured on solid media to confirm pure culture (growth takes up to 6 weeks) and for biochemical confirmation of *M. tuberculosis* and evaluation of in vitro susceptibility tests.

  – The sputum specimen is evaluated on liquid media, and the confirmation of *M. tuberculosis* and susceptibility testing is performed by molecular methodologies. The advantage is rapid identification and characterization of the liquid media isolate. However, clinical development programs that intend to use molecular methodologies to identify and characterize *M. tuberculosis* should also obtain solid media cultures in at least a subset of patients to evaluate the antimycobacterial susceptibility testing of the investigational drug(s), which can be used for determining susceptibility test criteria.

- **Using solid media for the baseline culture.** The sputum specimen is evaluated on solid media. The disadvantage is that mycobacterial growth takes up to 6 weeks for identification and characterization of *M. tuberculosis.*

Solid or liquid culture media can be used for the evaluation of patients on therapy and after therapy completion. Sequential negative culture results can be interpreted as no growth of *M. tuberculosis* as part of the endpoint assessments. Within a clinical trial, the culture methodologies should be consistent to evaluate all patients in the trial.

2. Relevant Nonclinical Safety Considerations

Combination therapy remains the standard of care for the treatment of tuberculosis. The nonclinical studies to characterize the safety profile of a combination regimen and to support clinical trials and approval of a marketing application will vary, depending on the information available on each separate drug and the intended patient population.[19] We encourage sponsors to discuss the available toxicology data and plans for combination therapies with the FDA.

The need for combination toxicology studies before administering a combination of investigational (unapproved) drugs to humans should be based on the following considerations:

[19] For guidance on when to conduct nonclinical combination studies to support clinical trials of drug combinations, see the following: (1) guidance for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations*; (2) ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*; and (3) ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.*

- The availability of clinical experience with the individual drugs

- The availability of nonclinical toxicology data for each of the individual drugs for the proposed duration of the combination clinical regimen

- The existence of a significant toxicological concern and the safety margin between the no observed adverse effects level for each of the individual drugs in the animal toxicology studies and the proposed human exposure to each of the investigational drugs in the combination

- The potential for interaction based on the absorption, distribution, metabolism, and excretion of each of the drugs

- The potential for adverse effects to involve the same organ system (*overlapping toxicities*) or synergistic toxicities based on a review of accumulated data from each of the investigational drugs

- The benefit derived from the drugs based on the degree of unmet need for the patients in the trial (e.g., patients with drug-resistant tuberculosis who have limited or no alternative therapies)

Although performance of nonclinical toxicology studies of the combination regimen of two or more early stage investigational drugs generally is recommended before initial use of the regimen in patients (e.g., ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*), sponsors should contact the FDA to determine if nonclinical toxicology studies of the specific investigational drug combination regimen would be needed.

3. PK/PD Considerations

a. Phase 1/phase 2 PK trials

The pharmacokinetics of the investigational drug should be fully characterized in single-dose PK, multiple-dose PK, and phase 2 PK/PD evaluations. Clinical pharmacology trials conducted during phase 1 and phase 2 drug development should include the characterization of PK in specific populations, including patients who have renal or hepatic impairment, as well as an evaluation of the effect on the QT interval.[20]

b. Drug interactions

In vitro studies should be conducted to determine the potential of the investigational drug to act as a substrate, inhibitor, or inducer of major human metabolizing enzymes and relevant transporters. Based on these results, in vivo drug interaction evaluations between one or more of

[20] See the ICH guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs; Questions and Answers (R1).*

the antimycobacterial drugs used in the planned treatment regimen, or for drugs unrelated to treatment of tuberculosis but are likely to be used (e.g., antiretroviral therapy for treatment of HIV; antacid therapy that can affect the gastrointestinal acid environment), may be needed before initiating clinical efficacy trials.[21] Consultation with the FDA is strongly recommended during drug development regarding appropriate drug interaction evaluations for a specific investigational drug, and, in particular, in situations where co-development of two or more investigational drugs is being planned.

c. Exposure-Response

Exposure-response relationships should be explored during early phases of drug development to aid in selection of optimal dosing strategies for evaluation in later trials.[22] Sponsors are encouraged to explore exposure-response relationships for both sputum and serum drug concentrations and markers of activity (e.g., the time-to-sputum conversion or sputum conversion rate at 2 months in patients with pulmonary tuberculosis). Evaluations of subpopulations in phase 3 efficacy trials can provide additional information about exposure-response relationships.

4. Labeling Considerations

The INDICATIONS AND USAGE section of the Full Prescribing Information should state that a drug is approved for the treatment of active pulmonary tuberculosis. For example:

'Drug X is indicated for the treatment of pulmonary tuberculosis'

For drugs approved under accelerated approval, additional information concerning the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits should be included in the indications and usage statement (see 21 CFR 201.57(c)(2)(i)(B)).

[21] See the draft guidance for industry *Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*. When final, this guidance will represent the FDA's current thinking on this topic.

[22] See the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*.

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APPENDIX:

JUSTIFICATION FOR A NONINFERIORITY MARGIN IN TREATMENT-SHORTENING CLINICAL TRIALS OF PULMONARY TUBERCULOSIS

This Appendix focuses on the analysis of the historical data and determining the HESDE for use in the justification for a noninferiority margin in clinical trials of treatment-shortening regimens for pulmonary tuberculosis. For complete discussion of noninferiority trials and justification of margins, see the draft guidance for industry *Non-Inferiority Clinical Trials.*[23]

For the purpose of defining a noninferiority margin, we considered the standard-of-care regimen to be 2 months of treatment with ethambutol (or streptomycin), isoniazid, rifampin, and pyrazinamide (intensive phase) followed by 4 months of treatment with isoniazid and rifampin (continuation phase), which is often described in abbreviated terminology as *2EHRZ/4HR* or *2SHRZ/4HR*. Additionally, we considered a daily to three-times weekly administration for the intensive phase to be part of a standard-of-care regimen, and we did not consider drugs given twice or once a week to be a standard-of-care regimen. We considered this standard-of-care regimen to be the active-controlled arm for a future noninferiority trial in drug-susceptible tuberculosis.

The endpoint of unfavorable outcome was defined as one of the following: (1) patients who never cleared their sputum to show no growth of *M. tuberculosis* while on therapy; (2) patients who had microbiological confirmation of relapse of pulmonary tuberculosis within a 12-month period of observation following therapy completion; or (3) patients who died any time within the clinical trial drug administration period and 12-month period of observation following therapy completion.

The use of a treatment-shortening regimen is intended to allow for the removal of at least several months of isoniazid and rifampin therapy (e.g., removal of the final 2 months (months 5 and 6) of isoniazid and rifampin therapy). It is the effect of these drugs during these months that we need to understand to estimate a treatment effect (M_1).

A full literature search found three trials that contained information directly related to the effects of rifampin and isoniazid in months 5 and 6. Two trials conducted by the British Medical Research Council (BMRC) were described in several articles, and there was one more recently conducted trial.

- In Study 1 (Singapore Tuberculosis Service/British Medical Research Council 1981; Singapore Tuberculosis Service/British Medical Research Council 1986) 360 patients 15 years of age and older who had pulmonary tuberculosis were randomized to one of four treatment groups:

  - Group A: Six-month regimen of 2 months of daily streptomycin, isoniazid, rifampin, and pyrazinamide followed by 4 months of isoniazid, rifampin, and pyrazinamide (**2SHRZ/4HRZ**)

[23] When final, this guidance will represent the FDA's current thinking on this topic.

- Group B: Six-month regimen of 2 months of daily streptomycin, isoniazid, rifampin, and pyrazinamide followed by 4 months of isoniazid and rifampin (**2SHRZ/4HR**)

- Group C: Four-month regimen of 2 months of daily streptomycin, isoniazid, rifampin, and pyrazinamide followed by 2 months of isoniazid, rifampin, and pyrazinamide (**2SHRZ/2HRZ**)

- Group D: Four-month regimen of 2 months of daily streptomycin, isoniazid, rifampin, and pyrazinamide followed by 2 months of isoniazid and rifampin (**2SHRZ/2HR**)

A comparison of groups A and B versus groups C and D provides an estimate of the treatment effect of isoniazid and rifampin when given in months 5 and 6 in the standard regimen. All patients were assessed at 18 months after enrollment. Deaths were not reported in the article.

- The second set of information (Study 2) comes from several publications of the BMRC's 4th and 5th East African Studies (East African/British Medical Research Council 1973; East African/British Medical Research Council 1978; East African/British Medical Research Council 1981; East and Central Africa/British Medical Research Council Fifth Collaborative Study 1983). The 4th East African/BMRC trial contained 5 4-month treatment groups, and enrolled patients 15 to 65 years of age who had drug-susceptible pulmonary tuberculosis. The bacteriological relapse rates were found to be unacceptably high and therefore the trial was halted earlier than planned. The last 193 patients enrolled in the trial were continued on their regimen for up to 6 months. These patients as well as newly enrolled patients were then included into the 5th East African study that did not contain 4-month treatment groups. Though the 4- and 6-month treatment arms are not concurrently randomized arms, the trials were conducted at similar sites and the protocols are believed to be similar between the 4th and 5th East African trials. The treatment groups of interest are listed here:

  - Six-month regimen of 2 months of daily streptomycin, isoniazid, rifampin, and pyrazinamide followed by 4 months of isoniazid and rifampin and (**2SHRZ/4HR** from the 5th East African study)

  - Four-month regimen of 2 months of daily streptomycin, isoniazid, rifampin, and pyrazinamide followed by 2 months of isoniazid, rifampin, and pyrazinamide (**2SHRZ/2HRZ**)

  - Four-month regimen of 2 months of daily streptomycin, isoniazid, rifampin, and pyrazinamide followed by 2 months of isoniazid and rifampin (**2SHRZ/2HR**)

  Deaths were reported in the article and are included as unfavorable outcomes.

- A third trial (Johnson, Haddad, et al. 2009) enrolled approximately 850 adults 18 to 60 years of age with noncavitary pulmonary tuberculosis who received the 2-month period of standard of care (i.e., 2EHRZ). All patients then received daily isoniazid and rifampin for an additional 2 months. At month 4, approximately 400 patients enrolled in the trial were eligible for randomization (all had negative sputum cultures at month 2) into one of two treatment groups: discontinue rifampin and isoniazid (shortened treatment course 2EHRZ/2HR) or continue rifampin and isoniazid for an additional 2 months (standard course of treatment 2EHRZ/4HR). Though the rate of unfavorable outcome was higher in the 4-month treatment arm (6.6 percent) than the 6-month treatment arm (1.5 percent), this trial enrolled only patients who had sputum conversion to no growth at 2 months and therefore represents a more limited patient population with potentially less severe pulmonary tuberculosis; it could therefore represent a conservative (low) estimate of the effect of the extra 2 months. The trial results might be less directly applicable to the overall population of patients with pulmonary tuberculosis and, therefore, were not included in the analysis.

Table A contains the results from Studies 1 and 2. Using the endpoint of failure to convert sputum to no growth, relapses of tuberculosis, and death at 18 months postrandomization (i.e., a period of time from randomization through 12 months following completion of the longer treatment arm), the 95 percent confidence interval (CI) of the weighted estimate of the treatment effect of rifampin and isoniazid for months 5 and 6 was (4.8 percent, 12.1 percent). Therefore, the estimate of M_1 is 4.8 percent. Without discounting any additional treatment effects, this supports a noninferiority margin of 4.8 percent.

Table A: The Results of Two Treatment-Shortening Studies[*]

Study	6-Month Regimen	Unfavorable Outcome	4-Month Regimen	Unfavorable Outcome	Treatment Effect (4-Month Regimen Minus 6-Month Regimen) and 95% CI
1	2SHRZ/4HR(Z)	1.2% (2/158)	2SHRZ/2HR(Z)	9.6% (15/156)	8.4% (3.8%, 14.2%)
2	2SHRZ/4HR	4.7% (8/172)	2SHRZ/2HR(Z)	13.2% (28/212)	8.6% (2.4%, 14.6%)
		Summary Estimate and 95% CI[**]			*8.4% (4.8%, 12.1%)*

[*] The number of deaths is unknown for Study 1 and therefore is not included in the outcome.
[**] Random effect model (DerSimonian and Laird 1986)

In a noninferiority trial in patients with drug-susceptible pulmonary tuberculosis where a treatment-shortening regimen is compared to a standard 6-month regimen, the selection of a noninferiority margin of 4.8 percent can be supported by the historical data and appears to be clinically acceptable. The clinical trial should incorporate the endpoint of failure to convert sputum to no growth, relapses of tuberculosis, or deaths at a 12-month period of observation following completion of the 6-month antituberculosis drug regimen. The work done on this noninferiority margin justification was presented at the 2009 FDA workshop.[24] A noninferiority margin for a treatment-shortening regimen has also been described (Nunn, Phillips, et al, 2008). Sponsors should discuss with the FDA the choice of a noninferiority margin greater than 4.8 percent and the scientific support for justification of the margin.

[24] The transcripts of the 2009 FDA pulmonary tuberculosis workshop can be found at http://www.fda.gov/Drugs/NewsEvents/ucm168975.htm.

A number of factors influence the estimate of a trial's sample size, including the prespecified type I and type II error rates, the expected success rates, and the noninferiority margin. The following example provides a framework for discussion with the FDA about sample size estimation for a noninferiority trial evaluating a treatment-shortening regimen (Makuch and Simon 1980). The total sample size of enrolled patients is approximately 480 patients per arm based on the following assumptions that can be considered conservative: (1) the identification of *M. tuberculosis* in 90 percent of enrolled patients (primary analysis population is approximately 430 patients per arm); (2) a two-sided type I error of 0.05 and power of 90 percent; (3) for both arms, a rate of 5 percent of patients who have the endpoint of failure to convert sputum to no growth, relapses of tuberculosis, or deaths at a 12-month period of observation; and (4) a noninferiority margin of 4.8 percent.