Concept Paper

Pulmonary Tuberculosis:
Developing Drugs for Treatment

Draft — Not for Implementation

This concept paper has been prepared by the Division of Special Pathogen and Transplant Drug Products, Office of Antimicrobial Products, in the Center for Drug Evaluation and Research at the Food and Drug Administration.

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Pulmonary Tuberculosis: Developing Drug Products for Treatment

1 INTRODUCTION

Developed for discussion purposes only, this concept paper reflects preliminary Agency thoughts regarding the overall development program and clinical trial designs for tuberculosis. We intend to solicit initial input from the public on this concept paper, and then develop a draft guidance for public comment according to the good guidance practices regulation (21 CFR 10.115).

2 BACKGROUND

Tuberculosis remains endemic in the United States and epidemic in many parts of the world. Global control of tuberculosis has long been a major public health challenge. Treatment of tuberculosis involves administering regimens of multiple drugs for a minimum of several months. Increasing resistance and multiple-drug resistance and the management of tuberculosis in immune compromised patients (e.g., persons with HIV/AIDS) have created new challenges in the management of tuberculosis. Safe and effective drugs with new mechanisms of action for the treatment of drug-resistant tuberculosis are needed. Drugs with improved safety profiles, drugs with fewer drug interactions (especially for patients needing concurrent treatment of HIV), and shorter course regimens also may contribute to efforts to manage tuberculosis.

Although this concept paper primarily focuses on the evaluation of single investigational drugs, the principles discussed are also generally applicable to the study of more than one investigational drug when used in combination.

3 PROPOSED DEVELOPMENT PROGRAM

The FDA’s preliminary thoughts on a drug development program for the treatment of tuberculosis are provided in the sections that follow.

3.1 GENERAL CONSIDERATIONS

3.1.1 Nonclinical Studies

Combination therapy remains the standard of care for the treatment of tuberculosis; consideration should be given during nonclinical pharmacology/toxicology development to studies of the investigational drug in combination with other approved drugs likely to be used as part of a treatment regimen. Carcinogenicity studies may need to be conducted if it is expected that patients will be treated with the drug for 6 months or longer. Likewise, nonclinical juvenile toxicity studies may be necessary before enrolling pediatric patients in treatment trials. In
addition, Segment I, II, and III reproductive and developmental toxicity studies may need to be completed before conducting clinical trials enrolling pregnant women.

Investigational drugs being studied for the treatment of tuberculosis should have supportive data from in vitro microbiology and in vivo animal model studies and should include multiple-drug regimens that contain the investigational drug. If two new drugs are under investigation simultaneously, factorial designs studying the new drugs should be considered. The mechanism of action of the drug should be identified to support its use as part of a specific clinical multiple-drug regimen. See section 3.3, Other Considerations, for additional information.

3.1.2 Early Phase Clinical Development Considerations

Before entering into phase 3 clinical trials, the activity of the investigational drug against *Mycobacterium tuberculosis* can be evaluated in early bactericidal activity (EBA) trials and/or trials that evaluate microbiologic outcomes at early time points.

3.1.2.1 Early bactericidal activity trials

EBA trials can provide information on the bactericidal activity of single drugs in clearing *M. tuberculosi*s from the sputum of patients with pulmonary tuberculosis. EBA trials do not provide direct information on the sterilizing activity of drugs. Because not all effective antimycobacterial drugs perform well in EBA trials, decisions to proceed with drug development should not be based on these results alone.

Even short-course monotherapy (e.g., 2 to 14 days of exposure) may result in the development of resistance to an experimental drug and may also result in disease progression. Because of concerns regarding resistance if trials use even brief periods of monotherapy, enrollment should be limited to immunocompetent, treatment-naïve adult patients at low risk of drug resistance and extrapulmonary disease so that an alternative treatment exists if clinical progression occurs during the trial.

3.1.2.2 Phase 2 trials

Trials designed to assess microbiological response at an early time point (e.g., at 8 weeks) may be useful for evaluating possible doses and/or regimens before initiating phase 3 clinical trials. Endpoints for such trials can include the following:

- Sputum smear conversion to the absence of acid fast bacilli (AFB) at a fixed early time point (e.g., 8 weeks)
- Sputum culture to no growth of *M. tuberculosis* at a fixed early time point
- Time to sputum smear conversion to negative for the presence of AFB, or time to no growth of *M. tuberculosis*
• The rate of reduction of viable *M. tuberculosis* by serial sputum colony forming units counts on culture

• Assessment of clinical endpoints during the trial (e.g., fever, weight gain)

3.1.3 **Efficacy Considerations**

Two adequate and well-controlled clinical trials usually will be needed to support a claim for a treatment indication for tuberculosis. A single clinical trial may provide sufficient evidence in certain limited circumstances (e.g., highly reliable and statistically conclusive evidence of an important clinical benefit such as improved survival), when confirmation of the result in a second trial would be practically or ethically impossible.¹

3.1.4 **Safety Considerations**

It is important to assess information on the safety profile of the drug when determining the populations for whom the investigational drug will be ultimately developed. Safety information from nonclinical studies and early clinical trials may be important in assessing the risks and benefits of the investigational drug and in selecting patient populations for whom the drug will be developed. Because of the limited treatment options and the high rate of morbidity and mortality for patients with drug-resistant tuberculosis, there may be situations where a drug’s safety profile might be appropriate for further development in patients with drug-resistant tuberculosis, but not for treatment of patients with drug-sensitive tuberculosis.²

3.1.5 **Drug Development Populations**

3.1.5.1 Pulmonary tuberculosis

The trial populations should include adults with pulmonary tuberculosis and when appropriate children and/or pregnant women with pulmonary tuberculosis (see section 3.2.10).

3.1.5.2 Pulmonary tuberculosis with sites of extrapulmonary involvement

This concept paper focuses on clinical trials in patients with pulmonary tuberculosis. Extrapulmonary disease may require longer durations of therapy than pulmonary tuberculosis and assessment of other endpoints that also evaluate the extrapulmonary site. The pharmacokinetic (PK) distribution of the investigational drug is an important consideration in assessing its usefulness for extrapulmonary tuberculosis (i.e., genitourinary tuberculosis may be

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¹ See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products* (http://www.fda.gov/cder/guidance/index.htm).

² The term *drug-sensitive tuberculosis* refers to strains of *M. tuberculosis* that are sensitive to first-line drugs for treatment: INH and rifampin. Multiple-drug-resistant tuberculosis refers to strains of *M. tuberculosis* that are resistant to INH and rifampin but are sensitive to most second-line drugs. Extensively drug-resistant tuberculosis refers to strains of *M. tuberculosis* that are resistant to INH and rifampin and at least three of the six main classes of second-line drugs (see Revised Definition of Extensively Drug-Resistant Tuberculosis, 2006, MMWR, 55(43):1176).
amenable for therapy with a drug primarily excreted by renal metabolism and central nervous system tuberculosis may not be amenable to therapy with a drug unless the drug penetrates into the central nervous system).

3.2 SPECIFIC EFFICACY TRIAL CONSIDERATIONS

3.2.1 Trial Design

To demonstrate efficacy, trials of investigational drugs for the treatment of tuberculosis can be designed to show that a regimen containing the investigational drug is either superior or noninferior to a reference regimen. Several possible clinical trial designs to evaluate efficacy are described below. Clinical trials must comply with applicable laws, regulations, and standards of care.3,4,5

3.2.1.1 Clinical trials designed to show superiority

The following trial designs can be considered to show superiority:

- One possible design is a two-arm trial where an investigational drug plus a background regimen is directly compared to placebo plus a background regimen. Efficacy can be demonstrated by showing superiority of the investigational drug plus a background regimen over the placebo plus a background regimen. Patients in both arms should receive a background regimen predicted to be active based on epidemiologic information and susceptibility testing data when available (see section 3.2.6, Choice of Comparator or Background Regimen). Placebo should be added to the background regimen in the comparator arm to maintain blinding.

- Trials that are enriched for or that enroll exclusively patients with drug-resistant tuberculosis may provide an opportunity to demonstrate superiority of a new investigational drug. Trials can enroll patients at risk for drug-resistant tuberculosis based upon epidemiological risk factors, or enroll patients with known drug-resistant tuberculosis that require a change to a new antimycobacterial regimen. In the setting of treatment for drug-resistant tuberculosis, the effect of the investigational drug plus background regimen may be more likely to demonstrate superiority over its background regimen. We anticipate that drug-resistant tuberculosis trials will use a background regimen that has been optimized.

- Trials that enroll patients with tuberculosis without using an enrichment strategy for drug-resistant tuberculosis can demonstrate efficacy by showing superiority of the

3 See 21 CFR parts 50, 56, and 312.


investigational drug plus background regimen over placebo plus background regimen. However, in the setting of predominantly drug-sensitive tuberculosis, it may be more challenging to demonstrate the added efficacy benefit of the investigational drug plus background regimen over the background regimen.

- Another possible design is a two-arm trial in which one component of a standard treatment regimen is replaced with an investigational drug in one arm of the trial and the other arm receives the standard regimen. Efficacy is demonstrated by showing superiority of the regimen that contains the investigational drug over the standard regimen.

- Dose-response trials where a higher dose (or more intensive regimen) is found to be superior to a lower dose (or less intensive regimen) are another means to demonstrate efficacy.

3.2.1.2 Clinical trials designed to show noninferiority

Noninferiority trials rely on historical data describing the effect size of the comparator drug that is being replaced within a regimen to establish an appropriate lower limit for the noninferiority margin. Defining a noninferiority margin for a component of a multiple-drug regimen based on previous trials may be challenging. Some drugs (e.g., ethambutol) may have little or no identifiable antimycobacterial effect when used in conjunction with drugs like rifampin for treatment of drug-sensitive tuberculosis; replacement of such drugs with an investigational drug may not provide evidence that the investigational drug is effective in a noninferiority trial. The basis for proposed noninferiority margins, justification for the noninferiority margin, and treatment regimens will be useful to understand in assessing a trial that is designed to show noninferiority.

Possible trials designed to show noninferiority as a means to evaluate efficacy are described below.

- Two-arm trials designed to show noninferiority where the investigational drug replaces a component of a standard multiple-drug regimen may be possible if a reliable noninferiority margin based upon the treatment effect of the component of the standard multiple-drug regimen that is replaced can be determined. Noninferiority would be demonstrated by showing that the effect of the investigational drug is within an appropriate margin based on the assessment of the quantitative contribution that the component of the multiple-drug regimen that has been replaced reliably provides within the regimen.

- Trials also can be designed to demonstrate that the replacement of a comparator drug can result in the shortening of the duration of an overall treatment regimen. For example, a trial where the investigational drug is added to a regimen or replaces a component of a standard regimen that is administered for 4 months would be compared to the standard regimen

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6 The treatment effect that the component of the standard regimen that is being replaced reliably contributes to the overall regimen should be determined to have the data upon which to derive an appropriate noninferiority margin. Based upon the available information, it may be difficult to characterize the contribution of one drug to the treatment effect in a trial replacing one component of a multiple-drug regimen in this population (see section 3.2.11, Statistical Considerations).
administered for 6 months. If the effect of the additional 2 months of the standard regimen can be determined, a noninferiority margin could be derived from the historical difference in treatment effect of 6 months versus 4 months of the standard treatment. Noninferiority would be demonstrated by showing that the 4-month regimen containing the investigational drug performs within a prespecified margin of the performance of the 6-month regimen where the margin is based upon the decrement of the performance of the 6-month regimen when only administered for a 4-month time period.\footnote{Nunn, AJ, PPJ Phillips, and SH Gillespie, 2008, Design Issues in Pivotal Drug Trials for Drug Sensitive Tuberculosis (TB), \textit{Tuberculosis}, 88(S1):S85-92.}

In addition to the clinical trial designs described above, there may be other designs or variations of the above designs that may be informative trial designs for evaluating the safety and efficacy of an investigational drug for the treatment of pulmonary tuberculosis. For example, an efficacy trial that evaluates two investigational drugs might use a factorial design.

### 3.2.2 Trial Populations

Although a specific trial may target patients more likely to have either drug-sensitive or drug-resistant strains of tuberculosis, patients are likely to be randomized and enrolled in trials before standard drug susceptibility test results are available. Well-designed trial protocols should specify how patients will be handled once drug 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 focus on contacts of drug-resistant tuberculosis cases, patients from areas with highly prevalent drug resistance, patients relapsing after previous treatment, and patients failing therapy.

Tuberculosis is more prevalent outside the United States and clinical trials for treatment of tuberculosis are likely to be conducted in foreign countries. Accordingly, relevant pharmacogenomic differences between the trial population and patients in the United States should be evaluated to the extent feasible. Depending on the overall drug development plan and the investigational drug under study, additional safety data may be necessary from patients in the United States. Biological samples for future exploratory investigations into the effect of genetic polymorphisms on the PK and pharmacodynamics (PD) of the investigational drug would be useful in understanding any differences in safety and efficacy, if observed.

### 3.2.3 Inclusion Criteria

Patients with pulmonary tuberculosis can be enrolled based upon the following findings:

- Presence of AFB on a sputum specimen or an approved rapid diagnostic test for tuberculosis (microbiological diagnosis of tuberculosis should be confirmed by culture from sputum obtained at the time of enrollment)
• Chest radiograph findings consistent with active pulmonary tuberculosis:
  − Cavitary lesion or lesions
  − Apical infiltrates
  − Hilar lymphadenopathy
  − New infiltrate

• A minimum of two out of the following signs or symptoms that have been present for at least 2 weeks:
  − Cough
  − One or more episodes of hemoptysis
  − Fever
  − Pleuritic chest pain
  − Weight loss
  − Night sweats

It would be useful for the protocol to specify whether patients likely to have drug-susceptible tuberculosis, drug-resistant tuberculosis, or both based on specific standard criteria will be targeted for inclusion. If rapid diagnostic tests are used for determining drug susceptibility, these results should be subsequently confirmed by culture.

3.2.4 Exclusion Criteria

The following patients likely will not allow satisfactory assessment of drug efficacy and generally should be excluded:

• Patients who have already received significant therapy for the current episode of active tuberculosis (unless enrolled in a trial of drug-resistant disease)

• Patients requiring the use of nonprotocol treatment with activity against *M. tuberculosis*

• Patients with significant concurrent illness that may affect assessment of outcome

• HIV-infected patients with low CD4 cell counts (e.g., below 50 cells/mm$^3$) when outcome is more likely to be affected by HIV disease than by tuberculosis

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

• Patients with extrapulmonary tuberculosis

3.2.5 Randomization, Stratification, and Blinding

Trials should be double-blinded and randomized unless there is compelling justification why blinding cannot be accomplished. Blinding can include the use of matching placebos, matching active comparators, or over-encapsulation.
Stratification by HIV status and the presence or absence of cavitary disease should be done. In multiple-drug resistance tuberculosis trials, patients can be stratified by the number of drugs to which the tuberculosis isolate is resistant.

### 3.2.6 Choice of Comparator or Background Regimen

The choice of comparator or background regimen depends on the patient population that will be enrolled (e.g., the likelihood of infection with susceptible or resistant strains of *M. tuberculosis*). In general, comparator regimens should be chosen that are approved and represent standard of care. Optimized background regimen for trials of predominantly drug-resistant tuberculosis should be based on epidemiologic information on susceptibility. The optimized background regimen should be modified based on results from susceptibility testing; in general, patients should be on three to four drugs to which there is in vitro susceptibility.\(^8,9\)

The protocol should provide detailed information on the comparator and background regimen and standardized criteria for how and when any changes can be made to the clinical trial regimen within the protocol. It is critical that both treatment arms of the trial be handled consistently to prevent differential handling of comparator or background therapy by treatment arm leading to a biased trial result. Protocols should prespecify the need for alternative treatment in the setting of clinical or microbiological failure, or when there are serious adverse reactions requiring the termination of one or more drugs.

### 3.2.7 Dose Selection

Target PK/PD parameters (e.g., AUC/MIC, \(C_{\text{max}}/\text{MIC}\), \(T > \text{MIC}\)) based on in vitro and animal models, results from early clinical trials (e.g., EBA trials and/or trials of clearing AFB from sputum at early time points), and results from exposure-response relationships should be considered in selecting a dose for phase 3 clinical trials.

### 3.2.8 Efficacy Endpoints

The primary endpoint should be as follows:

- Clinical and microbiological cure:
  - Clinical cure: complete resolution of clinical signs and symptoms of tuberculosis present on the inclusion criteria and absence of any new clinical signs or symptoms

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Microbiological cure: three sequential sputum cultures demonstrating no growth of \textit{M. tuberculosis}, followed by inability to produce sputum because of complete resolution of clinical signs and symptoms or maintenance of no growth on cultures of sputum

After the completion of antimycobacterial drug treatment, the period of observation for the primary efficacy endpoint of clinical and microbiologic cure depends on the patient population. However, all trials should plan for a 24-month period of observation demonstrating no evidence of recurrence of the clinical symptoms or microbiological relapse following completion of therapy.

- Clinical and/or microbiological failure:
  - Protocol-defined clinical progression of pulmonary disease or a new focus of extrapulmonary disease that requires either a change in antimycobacterial therapy or unanticipated surgical intervention
  - Signs and symptoms of active tuberculosis (pulmonary or new onset of extrapulmonary), including radiographic worsening compared to baseline findings, resulting in re-initiation of antimycobacterial therapy during follow-up\(^\text{10}\)
  - Death during treatment or follow-up
  - A sputum culture with growth of \textit{M. tuberculosis}:
    - After a specific time point defined in the trial
    - Failure to achieve a negative culture that results in a change in antimycobacterial therapy
  - Any growth of \textit{M. tuberculosis} from an extrapulmonary site during the trial

Patients whose infection is considered a clinical or microbiological failure during treatment should have therapy altered as appropriate; however, these patients should continue to be followed per protocol. In recurrent disease, attempts should be made to compare new isolates with baseline isolates to distinguish between relapse and re-infection using standardized methods.\(^\text{11}\) The method used should be standardized and validated for differentiating relapse from new infection. Total recurrence rate and the recurrence rate corrected for re-infection at the

\(^\text{10}\) In some circumstances there may be brief re-initiation of antituberculosis 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 patients in this situation as failures.

\(^\text{11}\) In recent years molecular tests have been developed for the detection of various \textit{M. tuberculosis} strains, identifying mutations, and assessing drug resistance in different geographic areas. These methods are mostly based on polymerase chain reaction using a small amount of DNA. However, these methods have not been standardized and validated for differentiating relapse from new infection. Details of the methods used and the performance characteristics of the assay in the laboratory where actual testing is done should be provided with the trial reports.
end of the follow-up period should be assessed in the patient population that initially achieved a clinical and microbiological cure at end of treatment.

Clinical trials should, in general, plan to follow patients for 24 months after treatment completion; in a treatment-shortening trial, this period would begin after the completion of treatment in the longest duration arm. The clinical and microbiological efficacy endpoints should be assessed at 6, 12, 18, and 24 months following completion of treatment. The timing of the primary endpoint assessment depends on the population enrolled in the clinical trial.

3.2.9 Trial Procedures and Timing of Assessments

We recommend the following procedures for pulmonary tuberculosis clinical trials.

At Entry

- Collect demographic information and medical history, including:
  - Underlying medical conditions
  - History of prior treatment for tuberculosis
  - History of treatment with immunosuppressive drugs
  - Results of previous HIV testing and CD4 cell counts (if applicable)
  - Previous HIV-associated opportunistic infections (if applicable)

- Baseline laboratory tests should include complete blood cell counts (CBC), liver function tests (e.g., serum albumin, alkaline phosphatase, serum aminotransferases, bilirubin, lactate dehydrogenase), renal function tests (e.g., serum creatinine, blood urea nitrogen, urinalysis), other serum chemistries (e.g., serum glucose, uric acid, phosphorous, potassium, amylase) HIV serology, CD4 cell count (if HIV positive), pregnancy test (in women of childbearing potential), 12-lead electrocardiogram, and other appropriate baseline tests.

- Chest imaging (standard posterior to anterior view and lateral chest radiographs, or CT scans if available) to assess the extent and severity of disease. Radiographic findings might be an important stratification criterion.

- Complete physical examination including vital signs and weight; depending on the regimens being investigated, additional targeted neurological examination and/or ophthalmological examination may be necessary.

- Sputum specimens for AFB smears and mycobacterial culture obtained by 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). Baseline isolates also should be stored for genotypic comparison with any later isolate in the event of emergence of drug resistance or re-infection.
During Trial Drug Administration

As a general rule, clinical assessments should occur weekly or bi-weekly during the first several months of therapy, followed by monthly assessments until the completion of trial drug administration.

- Assessment of drug compliance; directly observed therapy (DOT) is strongly recommended for all patients.

- History and complete physical examination specifically including assessment of each of the clinical signs and symptoms evaluated at enrollment (e.g., cough, episodes of hemoptysis, fever, pleuritic chest pain, weight loss, night sweats).

- Assessment of adverse events.

- Laboratory tests to monitor safety and evaluate clinical improvement (e.g., CBC, urinalysis, liver function tests, renal function tests, other serum chemistries, or other tests as appropriate).

- Sputum specimens for AFB smears and mycobacterial culture at least monthly until three consecutive specimen cultures are negative, one of which preferably should be an induced sputum specimen. Depending on the trial drug and design, a shorter interval between specimen collections (e.g., 2 weeks) may be appropriate for certain periods of the trial. To address the potential for resistance emerging while on treatment, drug susceptibility using standardized methods should be determined on select isolates obtained while on treatment.

- Imaging: serial chest radiographs are not necessary in patients with drug-sensitive tuberculosis when patients demonstrate continued clinical and microbiological improvement, but serial chest radiographs may be important in patients with drug-resistant tuberculosis. Imaging procedures should be standardized in the trial depending upon the target patient population that will be enrolled.

During Follow-Up after Trial Drug Treatment Is Completed

Clinical assessment should occur at a minimum of every 2 months for the first 6 months after trial drug is completed, followed by a minimum of every 3 months thereafter.

- History and complete physical examination specifically including assessment of each of the clinical signs and symptoms evaluated at enrollment (e.g., cough, episodes of hemoptysis, fever, pleuritic chest pain, weight loss, night sweats).

- Assessment of adverse events.

- Sputum specimens for AFB smears and mycobacterial culture: among patients who are still able to produce sputum specimens, specimens should be collected at least every 2 months for
the first 6 months; thereafter specimens should be obtained at 12, 18, and 24 months, at a minimum. Inability to produce sputum should be recorded.

- Imaging: a chest radiograph after completion of therapy to evaluate any change in radiographic findings over time. Radiographic improvement might be an important secondary endpoint, in which case a centralized, blinded assessment of radiographs using standard interpretive criteria is recommended.

3.2.10 Special Populations

3.2.10.1 Pediatric populations

Drug development programs for treatment of tuberculosis should include pediatric populations, when appropriate information is available to support enrollment of pediatric patients. Clinical presentations, diagnostic approaches, and responses to treatment can differ among pediatric patients with tuberculosis. Specifically, sputum may be more difficult to obtain and confirmation of pulmonary tuberculosis by gastric aspirates may be useful. Some clinical signs, such as persistent fever or weight loss, may be more prominent for pediatric case definitions, and extrapulmonary tuberculosis is more common among children under the age of 5 years. Formulations that permit appropriate dosing across pediatric age ranges should be developed to allow early inclusion of pediatric patients during drug development.

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. As a result of these requirements, in general, pediatric patients can be enrolled in trials if age-appropriate dosing of the investigational drug has been confirmed and sufficient safety and antimycobacterial activity data in adults are available.

- Pharmacokinetics. The PK of any new drug for tuberculosis should be evaluated across all age ranges of pediatric patients with tuberculosis; the exact ages to be studied can be specific to the drug under investigation, but in general should include:
  - Birth to 1 month
  - 1 month to < 2 years
  - 2 years to < 5 years
  - 5 years to < 12 years
  - 12 years to < 16 years

- Efficacy and safety. PK trials and safety trials in a sufficient number of pediatric patients with tuberculosis should be conducted if an extrapolation of adult efficacy to pediatrics for the treatment of pulmonary tuberculosis can be justified. If extrapolation is not feasible, for example in children under the age of 5 years where extrapulmonary tuberculosis is more common, efficacy and safety trials in a sufficient number of pediatric patients should be provided.

Sponsors should consider the timing of pediatric trials with respect to the overall drug development program. In addition, consideration should be given whether a data monitoring
committee (DMC) should be constituted for clinical trials that include children. In all trials involving children, institutional review boards and DMCs reviewing these trials should include members with relevant pediatric expertise to permit ongoing recognition and evaluation of safety concerns that arise during the course of the trial.\(^{12}\)

### 3.2.10.2 Pregnant women

Tuberculosis is common among women of childbearing potential in endemic areas, and drugs being developed for tuberculosis should address use during pregnancy. Currently, treatment of tuberculosis is recommended during pregnancy, both for the mother’s health and to prevent postpartum transmission to the infant.

Sponsors should consider the following factors when contemplating the possibility of enrolling pregnant women in clinical trials of an investigational drug to treat tuberculosis:

- Fetal risk considerations based on results from nonclinical studies and any available clinical data
- Available data about correct dosing in pregnant women (e.g., information from PK trials)
- Whether safety and efficacy have been demonstrated in nonpregnant populations
- Therapeutic options for the treatment of the pregnant patients with tuberculosis (the available therapeutic options may vary depending upon the presence of drug resistance)
- Ethical considerations for enrolling pregnant women in tuberculosis drug clinical trials based on maternal/fetal risk and benefit

The most appropriate time to study pregnant women during drug development may differ for a number of reasons. For example, the enrollment of pregnant women would have different risk benefit considerations for: (1) patients with drug-sensitive tuberculosis for whom known effective treatment is available versus drug-resistant tuberculosis where fewer therapeutic options are available; (2) trials of marketed drugs approved for other indications with experience of use in pregnancy versus investigational drugs with no prior marketing experience under development targeted solely for treatment of tuberculosis.

Before enrolling pregnant women in clinical trials evaluating drugs for the treatment of tuberculosis, nonclinical toxicology studies, reproductive toxicology studies, and phase 1 and phase 2 clinical trials should be completed. If the results from the nonclinical toxicology studies, reproductive toxicology studies, and phase 1 and phase 2 clinical trials are favorable upon review by the FDA, and treatment options are limited, it may be appropriate to characterize safety and pharmacokinetics in pregnant patients with tuberculosis who can benefit from the investigational drug. In situations when other safe and effective treatments for tuberculosis are available, based upon risk-benefit considerations, it may be more appropriate to complete phase 3 clinical trials to

\(^{12}\) See the ICH guidance for industry *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* (http://www.fda.gov/cder/guidance/index.htm).
establish safety and efficacy in nonpregnant patients before clinical trials in pregnant patients are initiated.

Depending upon the results from nonclinical studies, reproductive toxicology studies, and available information on safety and efficacy, information on dosing in pregnancy, and available treatment alternatives, women with tuberculosis who become pregnant while enrolled in trials for an investigational drug could be re-consented to remain in the clinical trial. In this setting, steady-state PK assessments, and safety and treatment outcomes can provide information to further evaluate correct dosing during pregnancy. Data to be collected in the above settings include the following elements: gestational age at enrollment; gestational timing and duration of drug exposure; and pregnancy outcomes including adverse maternal, fetal, and neonatal events. Infants born to mothers who received the investigational drug should be followed by investigators until at least 12 months of age.

3.2.11 Statistical Considerations

The issues specific to the determination of efficacy of an investigational drug for the indication of treatment of tuberculosis are discussed in this section.

3.2.11.1 Definition of analysis populations in tuberculosis trials

Analysis populations in tuberculosis trials are defined as follows:

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

- Modified intent to treat (MITT): all randomized patients with a positive culture for *M. tuberculosis* from a pretreatment sample. For some trials enrolling predominantly patients with drug-resistant tuberculosis, sponsors can consider an MITT population of all randomized patients with a positive culture for *M. tuberculosis* from a pretreatment sample documenting a drug-resistant phenotype. The MITT population for the primary analysis should be defined *a priori*.

- 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 and adherence to dosing regimens).

Efficacy should be assessed in the MITT analysis population, with safety assessed primarily in the ITT 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 and stated in the trial report. Loss to follow-up should be minimized because this should result in a better estimate of drug efficacy.

3.2.11.2 Covariates of interest

The following variables are of interest when analyzing results of a tuberculosis trial:
• Extent of pulmonary tuberculosis (i.e., cavitary versus noncavitary disease)
• HIV status
• Drug susceptibility to drugs in the treatment regimen
• Compliance (e.g., > 80 percent or < 80 percent of total regimen) (Note: DOT is strongly recommended for all patients)
• Center or region
• Age and sex
• Race and ethnic background
• Associated medical conditions
• Components of the optimized background treatment regimen
• Changes to the antimycobacterial treatment regimen during the trial
• Any factors not listed above that are used as baseline stratification factors

Analysis of treatment effect by these variables should be considered in the drug efficacy assessment; any differences or patterns observed based on these variables should be stated in the trial report. Patients can be stratified at randomization by the extent of pulmonary tuberculosis and/or HIV status to ensure balance between treatment arms on these factors.

3.2.11.3 Primary and secondary endpoints

The protocol should state the primary and secondary endpoints for the trial. Analyses should be performed to evaluate reasons for clinical and microbiological failure. Sponsors should provide the scientific evidence to support a proposed surrogate endpoint other than the rate of clinical and microbiologic cure. Such endpoints will need confirmation because they represent a durable clinical benefit.

3.2.11.4 Primary analysis

The primary analysis should be specified in the protocol together with any possible adjustments to the Type I error of the trial. If the trial is designed as a noninferiority trial, the noninferiority margin should be defined and justified a priori. The noninferiority margin justification should be included in both the protocol and the clinical trial report.

The comparison of the proportion of patients with a clinical and microbiological cure at the completion of the observation period should be the primary efficacy analysis. Patients who are lost to follow-up, have died, or have recurrent tuberculosis should be analyzed as failures in the primary analysis.

In patients with recurrent tuberculosis, the ability to distinguish between relapse and re-infection would be an important consideration.

3.2.11.5 Missing data

A challenge to patients and investigators is the adherence to follow-up visits during the observation period after completion of therapy. Therefore, the protocol should include
procedures for investigators to maximize data collection from all patients to minimize losses to follow-up and missing data during this time period. The protocol should state how missing data will be handled in the analysis. Additional methods of analyzing missing data should be included in the protocol or data analysis plan as secondary analyses; various methods should be consistent and help ensure lack of sensitivity of the trial conclusions to the type of method chosen. Given low failure rates in the treatment of drug-sensitive tuberculosis, missing data may confound the determination of efficacy. Significant amounts of missing data may render trial results inconclusive. Rates of missing data by treatment group should be compared, and if differences exist should be further explored and stated in the trial report.

3.2.12 Accelerated Approval (Subpart H) Considerations

Approval under 21 CFR part 314, subpart H, Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses, may be applicable to drugs developed for the treatment of tuberculosis that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

Sponsors should provide the scientific evidence to support a proposed surrogate endpoint (e.g., an endpoint based on conversion of sputum culture to no growth of *M. tuberculosis*) and analyses to be used for the purpose of accelerated approval at the stage that the protocol is being developed. When a drug is approved under 21 CFR 314.510 of Subpart H, sponsors are required to complete clinical trials to confirm the clinical benefit. Therefore, sponsors should plan to continue to evaluate safety and efficacy endpoints during the 24-month observation period after completion of therapy in the trials that supported accelerated approval. In addition, other trials might be recommended to confirm the clinical benefit.

3.2.13 Safety Considerations

To provide sufficient data on the safety of an investigational drug, the number of patients to be studied at the proposed dose and duration depends on a variety of factors including the risk-benefit for the indication, nonclinical toxicology concerns, clinical pharmacology findings, and clinical safety findings. Because tuberculosis is treated with a multiple-drug regimen, it is important that sufficient safety information be collected using the drug as part of the anticipated clinical regimen.

Study of special populations (i.e., geriatric patients, patients with renal insufficiency, and patients with hepatic impairment) should be included in the clinical safety database. Because of the high incidence of tuberculosis in patients co-infected with HIV, patients with HIV also should be included as part of the safety database.

The evaluation of the safety profile of an investigational drug for treating tuberculosis can be challenging because it is administered along with other antimycobacterial drugs and other concomitant medications (e.g., antiretroviral therapy for HIV) in patients who often have

13 See 21 CFR 314.510, Approval Based on a Surrogate Endpoint or on an Effect on a Clinical Endpoint other than Survival or Irreversible Morbidity.
comorbid conditions. Exploratory analyses of safety based on comparisons between patients that did and did not receive specific co-administered drugs may be informative.

A number of drug-related adverse events are common with standard antimycobacterial treatment regimens. These events include gastrointestinal upset, rash, drug fever, and hepatitis. Although it is reasonable to continue therapy for mild reactions of gastrointestinal upset, rash, and hepatitis (asymptomatic elevation of serum aminotransferases < 5x upper limit of normal), stopping therapy should be used for more severe reactions. Because many of the standard drugs for treatment of tuberculosis can cause these reactions, all drugs for treatment of tuberculosis including the investigational drug should be stopped simultaneously and restarted one at a time to explore which drug may be causing the reaction. The protocol should state the procedure for stopping and restarting antimycobacterial drugs and the order in which the drugs should be restarted.

Patients who require permanent discontinuation from the investigational drug should continue to be followed per protocol for outcomes (i.e., patients should remain in the trial even if off the investigational drug).

3.3 OTHER CONSIDERATIONS

3.3.1 Nonclinical Microbiology Considerations

Investigational drugs being studied for the treatment of tuberculosis should have supportive data from in vitro microbiology and in vivo animal model studies. Because clinical use of any new drug for the treatment of tuberculosis is in combination with other drugs, in vitro/in vivo testing should include some study of drug combination/regimens that contain the investigational drug. The mechanism of action of the drug should be identified to support its use as part of a specific clinical multiple-drug regimen.

3.3.1.1 In vitro studies

In vitro studies should include the following:

- Detailed studies of drug activity against metabolically active, dormant, and intracellular stages of *M. tuberculosis*. Testing against metabolically active bacilli should be conducted on drug-sensitive laboratory strains as well as laboratory strains with known patterns of resistance to currently approved tuberculosis drugs. These studies should identify the optimal in vitro concentration effective for inhibiting growth and/or killing of the organism during metabolically active and dormant stages. Appropriate positive and negative controls should be included in the study.

14 This process is discussed in *Treatment of Tuberculosis* (American Thoracic Society, Centers for Disease Control, and Infectious Diseases Society of America, 2003, MMWR 52(RR-11): 1-77).

15 If two new drugs are under investigation simultaneously, sponsors should consider factorial designs studying the new drugs.
• Study of drug activity against patient isolates preferably from representative geographic areas such as the United States, Asia, Europe, and Africa; this should include isolates from the regions where clinical trials are planned and should include drug-resistant strains.

In vitro studies should use standardized methods for susceptibility testing such as those recommended by Clinical Laboratory Standard Institute Document M24-A or by Antimicrobial Susceptibility Test systems approved by the FDA. If nonstandard methods are being evaluated, a complete description of the methods used and the performance characteristics of the assay in the actual laboratory where testing was done should be included when trial reports are submitted. Attempts should also be made to identify and designate quality control strains during testing and establishing of interpretive criteria/breakpoints. If interpretive criteria/breakpoints are established, then testing of at least 150 clinical isolates, preferably from representative geographic areas, should be included.

For all in vitro and in vivo studies, the criteria used for characterizing strains as drug susceptible or drug resistant should be specified.

3.3.1.2 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 design. Evaluations of the investigational drug using different animal models or more than one strain of M. tuberculosis should be considered for studying activity against different aspects of tuberculosis infection. Animal studies cannot substitute for the clinical trials in patients with tuberculosis that must be conducted to evaluate drug safety and efficacy because clinical trials can be conducted in patients with tuberculosis.16

3.3.1.3 Drug resistance and cross-resistance

The potential of M. tuberculosis strains to develop resistance 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.

3.3.2 Clinical Pharmacology Considerations

3.3.2.1 Phase 1 and phase 2 clinical PK trials

The PK/PD of the investigational drug should be fully characterized in single- and multiple-dose trials. Clinical pharmacology trials conducted during phase 1 and phase 2 drug development should include the following:

16 21 CFR part 314, subpart I
• Characterization of PK in healthy volunteers
• Characterization of PK in infected patients
• Characterization of the effect of food on PK
• Trials of PK in special populations, including patients with renal and/or hepatic impairment
• Trials of the effect of the investigational drug on the QT interval\textsuperscript{17}

Other trials may be appropriate based on the specific properties of the drug under investigation and/or findings from nonclinical studies.

3.3.2.2 Drug interactions

In vitro metabolism studies should be conducted to characterize the potential of the investigational drug as a substrate, inhibitor, and inducer of the human cytochrome P450 enzyme system; based on these results, in vivo drug interaction trials may be needed before initiating clinical efficacy trials. The interaction potential between the investigational drug and rifampin should be evaluated in healthy subjects and subsequently in infected patients, as appropriate. In addition, the effect of the addition or substitution of the investigational drug on the pharmacokinetics of the other drugs in a treatment regimen should be evaluated in a subset of infected patients, preferably under steady state conditions.

Additional drug interaction trials also may be appropriate for drugs unrelated to treatment of tuberculosis but likely to be used in infected patients (e.g., background anti-HIV therapy). Drug interaction trials should be completed before enrollment of HIV-infected patients to ensure there are no interactions with the investigational drug and drugs that may be used for HIV treatment. Depending on the physiochemical properties of the investigational drug, interaction trials with drugs that affect gastrointestinal acid environment (e.g., antacids, proton-pump inhibitors, histamine-2 receptor antagonists) also may be needed.

3.3.2.3 Exposure-response relationships

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. Sponsors are encouraged to explore exposure-response relationships for both sputum and serum drug concentrations and markers of activity (e.g., time-to-sputum conversion, sputum conversion rate at 2 months in patients with tuberculosis).\textsuperscript{18}

3.3.3 Labeling

Labeling will indicate that drugs are approved for the treatment of active pulmonary tuberculosis based upon the populations studied. For example:

\textsuperscript{17} See the ICH guidance for industry \textit{E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs} (http://www.fda.gov/cder/guidance/index.htm).

\textsuperscript{18} See the guidance for industry \textit{Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications} (http://www.fda.gov/cder/guidance/index.htm)
Drug X is indicated for the treatment of active pulmonary tuberculosis. This is based on trials in patients with [drug-susceptible and/or drug-resistant] tuberculosis where...

Drug X should be used in combination with other antimycobacterial agents for the treatment of adult patients who have evidence of infection due to *M. tuberculosis*.

3.3.4 Foreign Data

Data from clinical trials conducted abroad are likely to be used in support of a new drug application for a new antimycobacterial drug or regimen. Trials conducted in foreign countries can be used for drug approval when these trials meet FDA standards for the conduct and design of clinical trials. Foreign sites must be prepared to allow FDA auditing if requested.\(^\text{19}\) We recognize the challenges involved in conducting trials abroad, and the need to reconcile regulatory requirements with local laws and practices in countries where trials are conducted. Technical or financial constraints at foreign sites should be addressed by the sponsor during drug development to ensure that FDA regulations regarding clinical trials and good clinical practice are followed.

3.3.5 Fixed-Combination Drugs

Sponsors planning to develop a fixed-combination drug for the treatment of tuberculosis should describe how the development program will address the regulation on fixed-combination prescription drugs for humans under 21 CFR 300.50. The fixed-combination regulation states that the contribution that each component contributes to the claimed effect should be demonstrated.

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