Pulmonary Tuberculosis: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE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)

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Revision 1

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Pulmonary Tuberculosis: Developing Drugs for Treatment Guidance for Industry[1]

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of investigational drugs for the treatment of pulmonary tuberculosis (TB) under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355 and FDA regulations at 21 CFR part 312 and part 601.[2] Specifically, this guidance provides the FDA's current recommendations regarding the overall development program for a new investigational drug or drugs to be used in combination with approved drugs or as a new treatment regimen that includes one or more investigational drugs to support an indication for the treatment of pulmonary TB. This guidance does not address the development of drugs for latent TB infection or for extrapulmonary TB.

Sponsors should also refer to the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (June 2013).[3] Sponsors are encouraged to discuss with FDA the programs and pathways facilitating drug development that might be applicable for their development program.[4]

This guidance revises and replaces the draft guidance for industry of the same name issued in November 2013. This revision includes more detail regarding nonclinical models, early phase studies, and trial design considerations, including the demonstration of efficacy using superiority or noninferiority (NI) trial designs. Additionally, updates are made regarding inclusion of pediatric subjects in trials, endpoint and safety considerations, and labeling. The Appendix containing the NI margin justification has also been updated.

[1] This guidance has been prepared by the Division of Anti-Infectives in the Center for Drug Evaluation and Research 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] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics (May 2014).*

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the International Council for Harmonisation (ICH) guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001) (ICH E10), respectively.

In general, FDA's guidance documents 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

Infections caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) are diagnosed in the United States and are endemic in many parts of the world. Resistance to multiple drugs and coinfection with human immunodeficiency virus (HIV) pose challenges in the management of TB. Drugs with new mechanisms of action, improved safety profiles, fewer drug-drug interactions, and treatment-shortening combination regimens are needed to manage TB.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

Nonclinical evaluations provide valuable information for the development of investigational drugs (see section III.C.1., Microbiology Considerations, section III.C.2., Relevant Nonclinical Safety Considerations, and section III.C.3., PK/PD Considerations).

Activity of antimycobacterial drugs can be evaluated in trials of early bactericidal activity (EBA) and/or in phase 2 trials that evaluate microbiological outcomes at early time points. For a combination regimen, the sponsor should evaluate the contribution of each drug to the treatment effect.[5] This can be evaluated in phase 2 clinical development and in nonclinical studies (see section III.C.1., Microbiology Considerations). Treatment of pulmonary TB includes more than one drug in a treatment regimen, and sponsors may be developing more than one investigational drug as part of a new combination regimen. Sponsors should consult with the Agency early in development regarding plans to demonstrate the contribution of the investigational drug(s) as part of a combination regimen.

[5] The recommendations in this guidance are relevant to demonstrating the contribution of the individual new investigational drugs to the effect(s) of the combination regimen and are consistent with the requirements of 21 CFR 300.50, Fixed-combination prescription drugs for humans.

a. EBA

If applicable to the investigational drug under study, EBA trials evaluating the quantitative counts of viable *M. tuberculosis* from daily collections of sputum can provide information on the bactericidal activity of antimycobacterial drugs. These trials are intended to evaluate antimycobacterial activity of investigational drugs alone or in combination over a brief time course (e.g., 7 to 14 days). EBA trials can provide preliminary evidence for the contribution of each drug to the treatment effect of the combination regimen. Appropriate subjects for enrollment in EBA trials include immunocompetent subjects, treatment-naïve adult subjects at low risk of infection with drug-resistant TB, and subjects with no evidence of extra-pulmonary disease, who can begin standard-of-care treatment for pulmonary TB at the completion of the EBA trial.

b. Phase 2 evaluations

Sponsors should conduct phase 2 trials to assess the antimycobacterial activity of an investigational drug regimen. In addition, if feasible, a phase 2 development program should include a dose ranging study or studies to assist in determining the most appropriate dose regimen to be taken into phase 3. Phase 2 exploratory endpoints can include, but are not limited to, the following: (1) 8-week evaluation for absence of acid-fast bacilli (AFB) in sputum; (2) time to sputum culture negativity for *M. tuberculosis*; (3) symptom improvement; and/or (4) a biomarker intended to predict clinical benefit. The Agency recommends that as part of phase 2 trial designs, sponsors include long-term follow-up with collection of clinical endpoints in addition to earlier time points.

2. Efficacy Considerations

An investigational drug can be evaluated for efficacy when added to combination regimens of already approved drugs. Additionally, an entirely new combination regimen comprised of investigational drugs can be evaluated for efficacy. A single adequate and well-controlled trial in subjects with pulmonary TB, supported by other confirmatory evidence (e.g., evidence of antimycobacterial activity from nonclinical data, EBA, and phase 2 trials), may provide evidence of effectiveness when the single trial demonstrates a clinically meaningful and statistically robust treatment effect.[6] See section III., B., Specific Efficacy Trial Consideration, below for further discussion regarding efficacy considerations.

3. Safety Considerations

The evaluation of the safety profile of an investigational drug can be challenging because patients with pulmonary TB often have comorbid conditions. Sponsors should evaluate potential drug-drug interactions that may occur during coadministration with other antimycobacterial drugs or other concomitant medications (e.g., antiretroviral drugs).

[6] See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Hepatotoxicity and QT interval prolongation are common adverse reactions with antimycobacterial drugs. Sponsors should evaluate investigational drugs for their potential to cause hepatotoxicity, QT prolongation, and arrhythmias.[7, 8]

Sponsors should discuss the size of the preapproval safety database with the FDA during drug development. For assessment of risks and benefits in subjects with an unmet medical need, a smaller safety database of approximately 300 subjects treated at (or greater/longer than) the proposed intended dose and duration may be sufficient. If safety signals are identified, a larger safety database may be needed.

B. Specific Efficacy Trial Considerations

1. Trial Designs

Sponsors can use the following trial designs to demonstrate superiority:

- A regimen that includes one or more investigational drugs is compared to a standard regimen, with efficacy demonstrated by showing superiority of the investigational drug regimen over the standard regimen.[9]

- The investigational drug(s) plus the optimized background regimen (OBR) is compared to the matching placebo plus the OBR, with efficacy demonstrated by showing superiority of the investigational drug regimen over the placebo-containing regimen. Optimized background antimycobacterial treatment should be based on epidemiologic information and in vitro susceptibility testing, when available.

Sponsors can use the following trial designs to demonstrate NI:

- An investigational drug regimen is compared to a standard regimen. NI would be demonstrated by showing that the investigational regimen performs within a prespecified margin of the performance of the standard regimen.

- The investigational drug replaces one of the drugs in a standard combination regimen. The investigational drug regimen should perform within an acceptable NI margin that is based on the known quantitative and reliable contribution of the drug that has been

[7] See the guidance for industry *Drug-Induced Liver Injury: Premarketing Clinical Evaluation* (July 2009).

[8] See the ICH guidances for industry E14 *Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2005); E14 *Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs — Questions and Answers (R3)* (June 2017); S7B *Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals* (October 2005); and M3(R2) *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010).

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

replaced to the standard regimen. This NI trial design determines the efficacy contribution of the investigational drug to the regimen.

Interpretation of the results of an NI trial relies on a justified NI margin. This margin, which is highly dependent on the specific design of the NI trial, including the control regimen, is based, in part, on data from previously conducted trials to evaluate for historical evidence of sensitivity to drug effects (HESDE) and estimate the effect of the active control.[10] The Appendix contains an example of an NI margin justification for a trial of a 4-month regimen for drug-susceptible TB.

The FDA has not estimated an exact numerical treatment effect for the standard regimen of 2 months of treatment with ethambutol, isoniazid, rifampin, and pyrazinamide followed by 4 months of treatment with isoniazid and rifampin (abbreviated terminology: 2EHRZ/4HR) for patients with drug-susceptible pulmonary TB. However, considering the historical data on management and outcomes of patients with pulmonary TB in the era before antibacterial drug therapy and the highly successful results following treatment with 2EHRZ/4HR, there is support for the selection of an NI margin based on the large degree of clinical benefit. For example, given that the success rates of 2EHRZ/4HR exceed 90 percent, the numerical treatment effect is likely to far exceed 10 percent (Nahid et al. 2016). Therefore, based on clinical judgement, a 10 percent NI margin is clinically relevant and has appropriate preservation of the treatment effect for an NI trial to determine the efficacy of an investigational drug regimen as a whole based on comparison to this 6-month standard regimen.

Depending on the new investigational drug regimen, study design of the NI trial, potential impact (e.g., ability to fulfill an unmet medical need), and safety profile of the regimen, it may be appropriate to set a wider NI margin and still plan for a trial design that is feasible and provides a reasonable preapproval safety database. The Agency encourages sponsors to discuss their clinical trial designs and NI margin justifications with the FDA.[11]

For both superiority trials and NI trials that assess the activity of the investigational drug regimen as a whole, the sponsor will also need to address the added contribution of the components of the regimen.[9] This may be accomplished through nonclinical trials, EBA studies, phase 2 trials and/or as part of the pivotal efficacy trials.

2. Trial Population

The trial population should include adult subjects and if appropriate, pediatric subjects with pulmonary TB. The presence of extrapulmonary disease may require longer durations of treatment than pulmonary TB and assessment of endpoints that evaluate the extrapulmonary site(s). Trials can include subjects with either drug-susceptible or drug-resistant pulmonary TB depending on the anticipated effectiveness of the antimycobacterial drugs being evaluated.

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

[11] See also the article Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis (Gillespie et al. 2014).

Protocols should specify how subjects 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 regarding trials for drug-resistant TB can include a focus on contacts of subjects with drug-resistant TB, subjects from areas with a high prevalence of drug resistance, subjects who relapse after previous treatment, and subjects with disease progression on a standard regimen.

3. Inclusion and Exclusion Criteria

The FDA recommends the following inclusion criteria for subjects with pulmonary TB:

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

- Chest radiographic findings consistent with active pulmonary TB, for example, cavitary lesions, apical or other infiltrates, or hilar lymphadenopathy.

- A minimum of two of the following 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 or nonculture tests may help identify a subject for enrollment in a TB trial. If the tests being used are not FDA cleared, sponsors should provide sufficient information about the performance characteristics of the tests determined from analytical validation studies.

The FDA recommends the following as exclusion criteria for subjects with pulmonary TB:

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

- Significant concurrent illness other than HIV (e.g., lung cancer) that may affect outcome assessment

- Unwillingness to comply with recommendations from local public health authorities for the management of patients with pulmonary TB

4. Randomization, Stratification, and Blinding

Trials should be randomized and double-blind 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. If the trial cannot be fully blinded, the sponsor should maintain the maximum possible level of blinding within the trial with blinded assessors, blinded databases until database lock, etc.

Sponsors should consider stratification of subjects based on certain baseline characteristics (e.g., by the presence or absence of cavitary disease, HIV infection). The sponsor should include in the protocol a discussion of how the analyses will account for the stratified randomization.[12]

5. Specific Populations

a. Pediatric populations

The FDA encourages sponsors to begin discussions about their pediatric clinical development plans as early as is feasible. 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, sponsors can enroll pediatric subjects in trials if sufficient safety, antimycobacterial activity, pharmacokinetic (PK), and efficacy data in adult subjects are available and appropriate dosing regimens for pediatric subjects have been characterized.[13] Sponsors can include adolescent subjects with pulmonary TB in phase 3 clinical trials, if appropriate.[14]

Sponsors must submit pediatric study plans no later than 60 calendar days after the date of the end-of-phase 2 meeting or another time as agreed upon by the FDA and the sponsor unless the

[12] See the draft guidance for industry *Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products* (May 2021). When final, this guidance will represent the FDA's current thinking on this topic.

[13] For example, see the article Towards Earlier Inclusion of Children in Tuberculosis (TB) Drug Trials: Consensus Statements from an Expert Panel (Nachman et al. 2015).

[14] See the guidance for industry *Development of Anti-Infective Drug Products for the Pediatric Population* (December 2021).

investigational drug has been granted an orphan designation.[15] Pediatric formulation development should begin as soon as results from the adult phase 2b trials are known and the sponsor has determined an appropriate dosing regimen.

Extrapolation of adult efficacy for the treatment of pulmonary TB to pediatric populations is acceptable for most pediatric populations, with the exception of very young children, who have different clinical and pathophysiologic characteristics. Sponsors should provide PK and safety information in a sufficient number of pediatric subjects to support the appropriate dose for treatment of children with pulmonary TB. Cohorts for pediatric studies can be defined based on chronological age or weight-based criteria, particularly for oral drugs. Studies of drugs across the pediatric spectrum of ages/weights can be conducted in parallel rather than sequentially unless there are specific safety or PK properties that warrant a different approach. If existing animal studies have identified potential developmental concerns for target organs (toxicology or pharmacology), juvenile animal toxicity testing may be appropriate.[16, 17]

Pediatric development plans for new TB investigational drugs could include children living with HIV provided there are no safety or drug-drug interaction issues that cannot be managed.

Sponsors should discuss their pediatric development programs with the FDA, especially if they include very young children (e.g., those younger than 5 years of age) because of differences in clinical manifestations (e.g., increased likelihood of extrapulmonary disease) and pathophysiologic characteristics.

b. Pregnant females

Sponsors can include pregnant females in clinical trials once all female reproduction toxicity studies and the standard battery of genotoxicity tests have been conducted.[18] Infants born to female subjects who received the investigational drug(s) should be followed by investigators for an appropriate length of time; sponsors should discuss the duration with the FDA before trial conduct.[19]

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[15] See section 505B(e)(2)(A) of the FD&C Act (21 U.S.C. 355c(e)(2)(A)). For additional information, see the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020) and the ICH guidance for industry *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* (December 2000).

[16] See the guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products* (February 2006).

[17] We support the principles of the 3Rs (reduce, refine, and replace) for animal use in testing when feasible. We encourage sponsors to consult with the review division when considering using a nonanimal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

[18] See the draft guidance for industry *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials* (April 2008). When final, this guidance will represent the FDA's current thinking on this topic.

[19] For recommendations regarding treatment of women during pregnancy or breastfeeding, see the American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America guidelines for treatment of TB (Nahid et al. 2016), available at https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm.

c. Other specific populations

Sponsors should include in trials geriatric subjects,[20] subjects with renal insufficiency, diabetes mellitus, and subjects with hepatic impairment, if feasible. Because of the high incidence of TB in patients coinfected with HIV, subjects with HIV should be included in trials.

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 (see section III.C.1.a., In vitro studies) and animal models of TB, results from early clinical trials (e.g., EBA and/or trials of AFB clearance from sputum at early time points), and results from exposure-response evaluations. PK/PD evaluations should include evaluations based on free drug concentrations.

7. Choice of Comparators

The choice of comparator or background regimen depends in part on the subject population that the sponsor will enroll in the trial (e.g., the likelihood of infection with drug-susceptible or drug-resistant *M. tuberculosis*). In general, sponsors should choose comparator regimens that contain FDA-approved drugs and represent standard of care. Before trial initiation, sponsors should discuss with the FDA the use of comparator regimens based on local practice outside of the United States, or the use of drugs that are not FDA-approved.

8. Efficacy Endpoints

Sponsors can use the following efficacy endpoints in clinical trials of investigational drugs intended to treat pulmonary TB:

- **A primary clinical efficacy endpoint that is comprised of survival and evaluation of *M. tuberculosis* growth on serial sputum culture examinations at a fixed time point following randomization for all treatment arms and includes a period of follow-up after completion of the planned treatment period. The FDA defines clinical success and failure as follows:**

  Clinical success is assigned to subjects who are alive, achieved *M. tuberculosis* culture negativity on serial sputum examinations, did not experience relapse or recurrence of pulmonary TB, and otherwise did not meet a definition of clinical failure. In general,

[20] See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* (August 1994) and *E7 Studies in Support of Special Populations: Geriatrics: Questions and Answers* (February 2012).

protocol-defined serial sputum examinations should occur every 2 weeks or once a month during treatment, and every 3 months following completion of treatment.[21]

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

- Protocol-defined clinical progression of pulmonary disease during treatment
- Switch in antimycobacterial therapy because of tolerability issues or clinical progression of pulmonary TB
- Signs or symptoms of active TB, including radiographic worsening compared to baseline findings, resulting in reinitiation of antimycobacterial therapy during follow-up[22]
- Death during treatment or follow-up
- Growth of *M. tuberculosis* on sputum culture outlined as follows:
  - Failure to achieve *M. tuberculosis* culture negativity in serial sputum specimens during the treatment period
  - Failure to maintain culture negative status after a specific time point defined in the trial (in general, this is expected to be any time after two consecutive negative sputum cultures, taken at least 28 days apart) on therapy or in follow-up
- Any growth of *M. tuberculosis* from an extrapulmonary site during the trial

- **A surrogate endpoint based on results of *M. tuberculosis* sputum cultures during treatment.** Demonstration of treatment effect on sputum culture conversion from positive to negative during treatment, either as a time-to-conversion analysis or at a fixed time point (e.g., at 2 months from randomization), could be considered as surrogate endpoints reasonably likely to predict clinical benefit under the accelerated approval statutory and regulatory provisions.[23] Additional considerations related to accelerated approval regarding verification and description of clinical benefit, including the durability of the treatment effect are discussed in section III.B.11., Accelerated Approval Considerations. Sponsors should obtain serial cultures 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 sterile culture, verified by *M. tuberculosis* culture negativity in at

[21] The protocol-defined timing of serial examinations of sputum for culture may differ from clinical practice, which often depends on local treatment guidelines and respiratory isolation procedures.

[22] In some circumstances, antimycobacterial therapy may be restarted though 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 trial subjects in this situation as failures.

[23] Section 506(c) of the FD&C Act and 21 CFR 314.510 or 21 CFR 601.41.

least two subsequent consecutive sputum specimens taken at least 14 days apart (e.g., three consecutive negative sputum cultures). Sputum cultures can be evaluated on either solid or liquid media (see section III.B.11., Accelerated Approval Considerations).

- **Secondary and exploratory endpoints.** Sponsors should consider the following:

  — A well-defined and reliable evaluation of symptoms, which can be included in the clinical trial as a secondary or exploratory endpoint. Of note, symptom evaluation in certain patient populations may be more difficult to interpret, for example, among patients coinfected with HIV who experience immune reconstitution inflammatory syndrome or non-HIV-infected individuals with paradoxical reactions (Rangaka et al. 2012).

  — Molecular or other biochemical evaluations to ascertain whether a positive culture for *M. tuberculosis* after drug treatment represents relapse or reinfection (e.g., an exploratory endpoint analysis that treats relapse of the baseline *M. tuberculosis* infection as a failure of the original study treatment and treats reinfection with a new *M. tuberculosis* isolate as a success of the original study treatment).

9. Trial Procedures and Timing of Assessments

a. Entry visit

Sponsors should obtain baseline demographic information, current medications, and complete physical examinations at the entry visit. In addition, sponsors should obtain the following at entry:

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

- Baseline safety laboratory evaluations.

- HIV serology and, if HIV positive, viral load and CD4 cell count.

- Imaging results (standard posterior to anterior view and lateral chest radiographs or computed tomography scans) describing the extent and severity of pulmonary disease.

- 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 pediatric subjects). When applicable, baseline specimens for quantitative cultures should be collected in a standardized manner (e.g., single early morning induced sputum, pooled 24-hour sputum).

b. Visits during therapy and after therapy completion

In general, clinical assessments should occur weekly or biweekly during the first months of therapy, followed by monthly assessments until therapy completion. After completion of therapy, assessments should occur approximately every 3 months until the assessment of the primary efficacy endpoint is complete (e.g., at 12 months after randomization). 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, sponsors should obtain sputum specimens for AFB smears and culture at least monthly. 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.

If subjects are not able to expectorate sputum spontaneously at follow-up visits after therapy completion, sponsors should consider other methods to obtain sputum (e.g., sputum induction).

10. Statistical Considerations

In general, the sponsor should include in the protocol a detailed statistical analysis plan stating the trial hypotheses and the efficacy analysis methods.

Sponsors should consider the following definitions of analysis populations:

- **Safety population:** all subjects who received at least one dose of the investigational drug during the trial.

- **Intent-to-treat (ITT) population:** all randomized subjects.

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

- **Per-protocol population:** all randomized subjects with a positive culture from a pretreatment sample who achieve a prespecified level of compliance with the protocol (e.g., presence at all or a high percentage of follow-up visits).

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

All subjects should be followed completely for the duration of the trial even if they discontinue the investigational drug(s). Sponsors should make every effort to minimize the loss to follow-up

477 throughout the trial. Given that missing data are nonetheless likely to occur, the protocol should
478 state how missing data will be handled in the primary efficacy analysis. Additionally, the
479 statistical analysis plan should define additional methods for handling missing data. The study
480 report should include an assessment of the dependence of the trial results on the specific method
481 for handling missing data.
482
483 To improve the precision of treatment effect estimation and inference, sponsors should consider
484 adjusting for prespecified baseline factors that are anticipated to be prognostic of the outcome. If
485 randomization is stratified by baseline covariates, the analysis should account for the stratified
486 randomization.
487
488 *11. Accelerated Approval Considerations*
489
490 In some circumstances, approval under 21 CFR part 314, subpart H, or 21 CFR part 601, subpart
491 E, may be applicable to drugs developed for the treatment of TB that provide clinically
492 meaningful benefit over existing treatments. An endpoint based on conversion of sequential
493 *M. tuberculosis* sputum cultures to negative (e.g., percent conversion at a prespecified time
494 point) can be used as a surrogate endpoint that is reasonably likely to predict clinical benefit
495 (Wallis et al. 2010; Wallis et al. 2013; Phillips et al. 2013; Wallis, Peppard, and Hermann 2015;
496 Wallis and Peppard, 2015; Phillips et al. 2016; Meyvisch et al. 2018). A sponsor may consider
497 other surrogate endpoints (e.g., biomarkers) that are also reasonably likely to predict clinical
498 benefit. When a drug is approved under accelerated approval, FDA will require that the sponsor
499 "study the drug further, to verify and describe its clinical benefit"[24] including the durability of
500 the treatment effect. Sponsors considering sputum culture conversion or other surrogate
501 endpoints that are reasonably likely to predict clinical benefit should consult with the Agency as
502 the clinical trial is being planned.
503
504 **C. Other Considerations**
505
506 *1. Microbiological Considerations*
507
508 Sponsors of investigational drugs being evaluated for the treatment of TB should have supportive
509 data from in vitro and in vivo (animal model) microbiological studies. These studies may
510 provide data to inform selection of the regimen of antimycobacterial drugs to be evaluated in
511 clinical trials and to assess the contribution of each drug to the investigational drug regimen.
512
513 a. In vitro studies
514
515 In vitro studies should encompass the following:
516
517 • Investigations of drug activity (inhibiting growth or killing) against metabolically active,
518 dormant, and intracellular stages of *M. tuberculosis*.
519

[24] 21 CFR 314.510 for drugs and 21 CFR 601.41 for biological products.

- Susceptibility testing against metabolically active bacilli from drug-susceptible laboratory strains, laboratory strains with known patterns of drug resistance, and clinical isolates representing different geographical regions.

- Standardized methods for susceptibility testing such as those recommended by the Clinical Laboratory Standards Institute (CLSI).[25]

- If nonstandard methods are being employed in the trial, prior submission for FDA review of a complete description of the methods and the performance characteristics of the assay in the actual laboratory where testing will be done.

- Establishment of quality control parameters for susceptibility testing before determination of in vitro activity.[26]

If two or more new investigational drugs are under evaluation simultaneously, the sponsor should conduct factorial design studies evaluating the new investigational drugs and provide the results to the FDA.[9] The FDA encourages testing against multiple strains of *M. tuberculosis*. See section III.C.3.d., In vitro hollow fiber system models, for methods of assessment of the contribution of individual drugs in a combination regimen.

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 clinical trials. PK assessments and changes in drug susceptibility in animal model studies may inform clinical trial designs. Sponsors should consider evaluations of the investigational drug, and/or combinations of investigational drugs, using different animal models and more than one strain/isolate of *M. tuberculosis* to study mycobacterial burden and sterilizing activity. In vivo studies conducted using a factorial design using clinically relevant exposures can provide information on the contribution of the individual drugs to the combination regimen.

c. Drug resistance and cross-resistance

Sponsors should examine the potential of *M. tuberculosis* isolates to develop resistance to the investigational drug in appropriate in vitro and/or animal models and should evaluate the potential for cross-resistance to drugs in the same class or in other classes used for the treatment of TB. If resistance is demonstrated, it is important to identify the mechanism(s) of resistance.

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[25] For examples, see the guidance for industry and FDA *Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems* (August 2009) and CLSI's Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard — Third Edition, (available at https://clsi.org/standards/products/microbiology/documents/m24/). For the most recent version of a class II special controls guidance document, check the FDA class II special controls guidance document web page at https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/class-ii-special-controls-documents.

[26] For more details, see the guidance for industry *Microbiology Data for Systemic Antibacterial Drugs — Development, Analysis, and Presentation* (February 2018).

Sponsors should attempt to evaluate the clinical significance of any changes in phenotype (e.g., in vitro susceptibility to the investigational drug) or genotype observed in nonclinical studies by correlating such changes with efficacy outcomes.

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

Solid media (e.g., Löwenstein-Jensen medium, Middlebrook 7H10 or 7H11 agar media) and liquid media (e.g., mycobacteria growth indicator tube) are culture assay methods used to identify and characterize *M. tuberculosis*. Sponsors can include other newer molecular methodologies to detect *M. tuberculosis* and its susceptibility profile in trials for microbiological evaluations. Sponsors should specify the methods used to culture and identify *M. tuberculosis* as well as the in vitro susceptibility testing methods that will be employed in the trial.

For baseline evaluations, the Agency recommends using both solid and liquid media. The advantages to this approach are (1) more rapid observation of mycobacterial growth in liquid media (e.g., less than 2 weeks) and (2) that growth of pure culture on solid media is already underway for (a) the biochemical confirmation of *M. tuberculosis* and (b) the evaluation of in vitro susceptibility.

For the evaluation of subjects on treatment and after treatment completion, sponsors can use solid or liquid culture media. Within a clinical trial, the culture methodologies among trial sites should be consistent to evaluate all subjects in the trial. Other types of culture evaluations can be informative as secondary or exploratory endpoints (e.g., quantitative culture techniques).

e. Differentiate relapse from reinfection or new infection

As a secondary analysis, sponsors should aim to utilize molecular methods to evaluate whether clinical failure is caused by relapse of the original infection or by development of a new infection, especially in subjects living in endemic areas. If any of these methods are used in a clinical trial, the sponsor should include details of the methods used as well as performance characteristics of all assays in the clinical protocol.

2. Relevant Nonclinical Safety Considerations

Combination regimens remain the standard of care for the treatment of TB. Individual drugs may be developed for treatment of active disease although they would be used as part of a combination regimen. Nonclinical studies to characterize the safety profile of individual drugs or a combination regimen and to support clinical trials and approval of a marketing application will vary, depending on the information available on each drug and the intended patient population.[27] The Agency encourages sponsors to discuss with the FDA the available toxicology

[27] For guidance on when to conduct nonclinical combination studies to support clinical trials of combination regimens, see the following: (1) guidance for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations* (March 2006); (2) ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*; (3) ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012); and (4) guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination*.

data for each investigational drug and a proposal for the clinical development of the combination regimen.

Sponsors should conduct nonclinical toxicology studies of a combination regimen consisting of two or more investigational (unapproved) drugs before initial administration of that combination regimen to humans based on the following:

- The availability of clinical experience with the individual drugs
- The availability of relevant nonclinical toxicology data for each of the individual drugs for the proposed duration of the combination regimen
- The existence of a significant toxicological concern and the safety margin between the no observed adverse effects level (NOAEL) 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 regimen
- The potential for drug-drug interactions 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

Sponsors should discuss with the FDA the type, duration, and timing of nonclinical toxicology studies needed to support clinical development of the combination regimen.

3. PK/PD Considerations

a. Phase 1/phase 2 PK trials

The PK of the investigational drug should be fully characterized in single-dose PK, multiple-dose PK, and phase 2 PK/PD evaluations. The FDA recommends characterization of PK in specific populations, including subjects who have renal or hepatic impairment, as well as an evaluation of the drug effect on the QT interval.[28]

b. Drug interactions

Sponsors should conduct in vitro studies to determine the potential of the investigational drug to act as a substrate, inhibitor, or inducer of major human metabolizing enzymes and relevant transporters.[29] Based on these results, drug interaction evaluations between one or more of the

[28] 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)* (October 2012).

[29] See the guidance for industry *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020).

antimycobacterial drugs used in the planned combination regimen, or with drugs unrelated to the treatment of TB but likely to be used concomitantly for other indications (e.g., antiretroviral therapy for treatment of HIV; antiviral therapy for treatment of hepatitis B or C), may be needed before initiating clinical efficacy trials.[30] The Agency strongly recommends that sponsors consult the FDA during drug development regarding appropriate drug interaction evaluations.

c. Exposure response

Sponsors should explore exposure-response relationships during early phases of drug development to aid in the selection of optimal dosing strategies for evaluation in later trials.[31] The FDA encourages sponsors 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 subjects with pulmonary TB).

d. In vitro hollow fiber system models

The results from hollow fiber system models, combined with other sources of nonclinical data, can help inform the selection of antimycobacterial drug regimens to begin clinical evaluation (Chilukuri et al. 2015). The hollow fiber system models can be used to simulate PK characteristics of drugs intended to treat TB and allows for the exploration of concentration-effect relationships potentially relevant to the treatment of TB in the clinical setting. These models are expected to provide key information on regimen selection for further evaluation. These models may also play an important role in evaluating the contribution of each drug (at clinically relevant exposures) to the treatment effect.

4. Foreign Clinical Data[32]

FDA regulations permit the acceptance of foreign clinical trials in support of a new drug application (NDA) or biologics license application (BLA) approval (21 CFR 312.120).

5. Data standards for TB

Study data standards describe a standardized way to exchange clinical and nonclinical research data between computer systems. Data standards have been developed for TB to provide a

[30] See the guidance for industry *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020).

[31] See the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* (April 2003).

[32] See the guidance for industry and FDA staff *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions* (March 2012).

consistent general framework for organizing study data, including templates for datasets, standard names for variables, and standard ways of doing calculations with common variables.[33]

6. Labeling Considerations

Generally, the labeled indication should reflect the patient population enrolled in the clinical trials. For example, sponsors should consider the following:

> Drug X is indicated in combination with Drugs Y and Z for the treatment of pulmonary tuberculosis.
>
> or
>
> Drug X is indicated in combination with other antimycobacterial drugs for the treatment of pulmonary tuberculosis.

For drugs approved under accelerated approval, the sponsor must include additional information in the INDICATIONS AND USAGE section (see 21 CFR 201.57(c)(2)(i)(B)).[34] For drugs approved under the limited population pathway for antibacterial and antifungal drugs, additional information is available for specific labeling requirements and recommendations.[35, 36]

[33] See, for example, the TB Therapeutic Area User Guide version 2 available at https://www.cdisc.org/standards/therapeutic-areas/tuberculosis/tuberculosis-therapeutic-area-user-guide-v2-0 and FDA's Study Data Standards Resources web page available at https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm.

[34] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics.*

[35] See section 506(h)(3)(A) of the FD&C Act (as amended by the 21st Century Cures Act).

[36] See the guidance for industry *Limited Population Pathway for Antibacterial and Antifungal Drugs* (August 2020).

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APPENDIX
Example of a Justification for a Noninferiority Margin in a Treatment-Shortening Clinical Trial of Pulmonary Tuberculosis

This appendix provides an example of a noninferiority (NI) margin justification. As stated in this guidance, NI margin justifications are dependent on the specific design of the NI trial. This justification is for a specific NI trial that would compare an investigational drug regimen consisting of a new investigational drug plus the first 4 months of the standard regimen to the standard 6-month regimen in subjects with drug-susceptible tuberculosis (TB). The effect of the investigational drug essentially replaces the effect of Months 5 and 6 of the standard regimen. Using historical data, this justification determines the effect of these 2 months of therapy (historical evidence of sensitivity to drug effects (HESDE)) to determine if the new investigational drug is effective based on the results of the NI trial. Additional information is available regarding a complete discussion of NI trials and justifications of margins.[1]

We identified two trials that allowed for an estimate of the effect of Months 5 and 6 in the standard regimen for drug-susceptible TB, based on a comparison of the standard-of-care regimen (2 months of treatment with ethambutol (or streptomycin), isoniazid, rifampin, and pyrazinamide followed by 4 months of treatment with isoniazid and rifampin, which is often described in abbreviated terminology as *2EHRZ/4HR* or *2SHRZ/4HR*) to a 4-month regimen of *2EHRZ/2HR* or *2SHRZ/2HR*.[2] The endpoint of unfavorable outcome was defined as one of the following: (1) subjects who never become sputum culture negative for *M. tuberculosis* while on therapy; (2) subjects who had microbiological confirmation of relapse of pulmonary TB within a 12-month period of observation following therapy completion; or (3) subjects who died at any time within the clinical trial drug administration period and 12-month period of observation following therapy completion.

Table A, below, contains the results from the two trials among subjects randomized to receive the 6-month regimen or the 4-month regimen. A comparison of the two regimens gives an estimate of the effect of the final 2 months of the 6-month regimen of 8.4 percent with a lower bound of the 95 percent confidence interval of 4.8 percent; 4.8 percent can be used as a conservative estimate of the treatment effect of Months 5 and 6 of treatment.

[1] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[2] See Singapore Tuberculosis Service/British Medical Research Council 1986; East and Central Africa/British Medical Research Council Fifth Collaborative Study 1983; and East African/British Medical Research Council 1981.

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%)*

[*] CI = confidence interval; 2SHRZ/4HR(Z) = 2 months of treatment with streptomycin, isoniazid, rifampin, and pyrazinamide followed by 4 months of treatment with isoniazid and rifampin (and pyrazinamide); 2SHRZ/2HR(Z) = 2 months of treatment with streptomycin, isoniazid, rifampin, and pyrazinamide followed by 2 months of treatment with isoniazid and rifampin (and pyrazinamide).

[**] The number of deaths is unknown for Study 1 and therefore is not included in the outcome. The 6-month and 4-month regimens in Study 2 are from separate trials; however, they were similarly designed and conducted, and occurred close in time. Study 1: Singapore Tuberculosis Service/British Medical Research Council, 1986, Long-Term Follow-up of a Clinical Trial of Six-Month and Four-Month Regimens of Chemotherapy in the Treatment of Pulmonary Tuberculosis, Am Rev Respir Dis, 133(5):779–783. Study 2: East and Central Africa/British Medical Research Council Fifth Collaborative Study, 1983, Controlled Clinical Trial of 4 Short-Course Regimens of Chemotherapy (Three 6-Month and One 8-Month) for Pulmonary Tuberculosis, Tubercle, 64(3):153–166; and East African/British Medical Research Council, 1981, Controlled Clinical Trial of Five Short-Course (4-Month) Chemotherapy Regimens in Pulmonary Tuberculosis, Am Rev Respir Dis, 123(2):165–170.

[***] Random effect model per DerSimonian, R and N Laird, 1986, Meta-Analysis in Clinical Trials, Controlled Clin Trials, 7(3):177–188.

In an NI trial in subjects with drug-susceptible pulmonary TB where a treatment-shortening regimen is compared to a standard 6-month regimen, the selection of an NI margin of 4.8 percent can be supported by the historical data. The NI margin justification presented here is a modification of the justification presented in Nunn et al. 2008.[3]

Although an NI margin of 4.8 percent may seem overly conservative, the fact that a very high proportion of subjects achieve a successful primary efficacy outcome with standard of care provides for a reasonable estimate of the sample size for an NI trial. Additionally, given the high proportion of subjects achieving a successful outcome, there is interest in maintaining this high proportion in new investigational drug regimens. For example, we identified a trial (Johnson et al. 2009)[4] that described halting of the trial by a data monitoring committee based on an approximately 5 percentage point estimate difference between the standard regimen and a treatment-shortening regimen, indicating that there is a clinical expectation that there should be a high proportion of subjects achieving successful outcomes in both treatment groups, making the selection of an NI margin of 4.8 percent a feasible consideration.

[3] Nunn, AJ, PPJ Phillips, and SH Gillespie, 2008, Design Issues in Pivotal Drug Trials for Drug Sensitive Tuberculosis (TB), Tuberculosis; 88(Suppl 1):S85–S92.

[4] Johnson, JL, DJ Hadad, R Dietze, et al., 2009, Shortening Treatment in Adults With Noncavitary Tuberculosis and 2-Month Culture Conversion, Am J Respir Crit Care Med, 180(6):558–563.

The following example provides a framework for discussion with the FDA about sample size estimation for an NI trial evaluating a treatment-shortening regimen (Makuch and Simon 1980).[5] The total sample size of enrolled subjects is approximately 480 subjects per arm based on the following assumptions: (1) the identification of *Mycobacterium tuberculosis* in 90 percent of enrolled subjects (primary analysis population is approximately 430 subjects 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 subjects who have the endpoint of failure to convert to negative sputum cultures, or who experience relapse of TB, or death at a 12-month period of observation; and (4) an NI margin of 4.8 percent.

Sponsors should discuss with the FDA appropriate NI margins for specific NI trials being proposed.

[5] Makuch, RW and RM Simon, 1980, Sample Size Considerations for Non-Randomized Comparative Studies, J Chron Dis, 33(3):175–181.