Bringing New TB Drugs to Market: A Regulatory Perspective

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Regulatory Best Practices for Global Access to Medicines, Including Anti-TB Medicines

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Outline

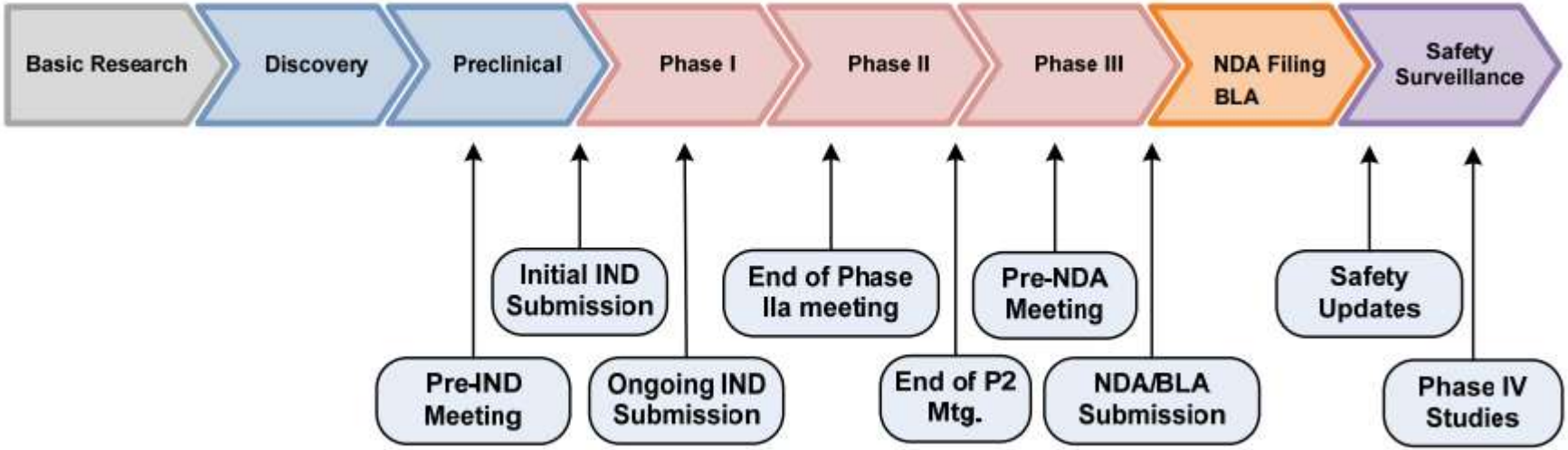
- Overview of FDA-approved drugs for treatment of **pulmonary** tuberculosis
- Regulatory pathways used and designations granted by FDA
- Clinical trial design considerations for TB

Overview of Drugs for Tuberculosis Treatment

FDA-Approved Drugs	Approval Year
Streptomycin	1946
PAS	1950
Isoniazid	1953
Pyrazinamide	1959
Cycloserine	1964
Ethionamide	1965
Ethambutol	1967
Rifampin	1971
Capreomycin	1971
Rifapentine	1998
Bedaquiline	2012
Pretomanid (with bedaquiline and linezolid)	2019

FDA-Approved Drugs Used Off-label for TB
Rifabutin
Levofloxacin
Moxifloxacin
Amikacin

Overview of Drug Development



"Overview of the Sequence of Drug Development Activities: PDUFA Activities in Drug Development"
https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/new-drug-development-and-review-process

Regulatory Pathways and Designations

- **Approval Pathways**
  - **Traditional:** Based on:
    - **Clinical endpoint** measuring how a patient feels, functions, survives or
    - **Validated surrogate endpoint**, e.g., viral load for HIV
  - **Accelerated:** Expedited pathway based on **a surrogate endpoint** that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality [21 CFR 314.500, (Subpart H)

Regulatory Pathways and Designations

- **Expedited Programs/Designations***: to facilitate development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition
  - **Fast Track Designation**
  - **Breakthrough Therapy Designation**
  - **Priority Review**
- **Qualified Infectious Disease Product Designation (QIDP)**
- **Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD)**

*https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics

Overview of Expedited Programs

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Nature of program	**Designation**	**Designation**	**Approval Pathway**	**Designation**
Qualifying[1] Criteria	**Breakthrough Therapy clinically significant endpoint:** Endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of disease. It includes effects on an established surrogate endpoint that could support traditional approval, or that is considered reasonably likely to predict clinical benefit (accelerated approval standard), OR a significantly improved safety profile		Provides meaningful advantage over available therapies AND demonstrates an effect on a **surrogate endpoint** reasonably likely to provide clinical benefit OR on a **clinical endpoint** that can be measured earlier than irreversible morbidity and mortality (IMM) that predicts an effect on IMM	Drug would provide a significant improvement in safety and effectiveness OR Supplement for labeling changed based on pediatric studies OR Application for a QIDP, OR Drug with a priority review voucher
Timing of Request			During development; confirmatory trials should usually be underway at the time of approval	With BLA, NDA or efficacy supplement

[1]**Treatment of a serious condition is a qualifying criterion for all expedited programs;** [2]Qualified Infectious Disease Product; [3]End of Phase 2
21 CFR part 314.500, subpart H; 21 CFR part 601, subpart E ; Section 506(c) of the FD&C Act as amended by section 901 of FDASIA https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

Overview of Expedited Programs

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Timelines for FDA Response	60 Days	60 Days	Not specified	60 Days
Features	• Actions to expedite development and review • Rolling review	• Intensive guidance on efficient drug development • Organizational commitment • Rolling review • Actions to expedite review	Approval based on an effect **on a surrogate endpoint or an intermediate clinical endpoint** that is reasonably likely to predict a drug's clinical benefit	Shorter clock for review of marketing application (6 months compared with the 10-month standard review)
Additional Considerations	Designation may be rescinded if it no longer meets the qualifying criteria for fast track	Designation may be rescinded if it no longer meets the qualifying criteria for breakthrough therapy	• Confirmatory trials to verify and describe the anticipated effect on IMM or other clinical benefit • Subject to expedited withdrawal if no benefit	Designation will be assigned at the time of original BLA, NDA, or efficacy supplement filing

Qualified Infectious Disease Product (QIDP*) Designation

- Antibacterial or antifungal drug for human use intended to prevent or treat serious or life-threatening infections
- Applies to a specific drug product (not drug substance, biologics or device) from a specific sponsor for a specific use
- Designation can be requested at pre-Investigational New Drug (pre-IND) and IND stage
- Provides the following incentives:
  - Additional 5 years marketing exclusivity for certain drugs
  - Priority review for the first application for a QIDP
  - Eligibility for Fast Track designation

*GAIN Provision (Title VIII of FDASIA under section 505E of the Food, Drug &Cosmetic Act):
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM594213.pdf; https://www.fda.gov/media/110982/download

Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD)

- For drugs that are intended to treat a serious or life-threatening infection in a limited population of patients with unmet need (FD&C Act, section 506(h)(8))
- Streamlined clinical development program for a limited population may involve smaller, shorter or few clinical trials
- Statutory standards for safety and effectiveness must be met

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/limited-population-pathway-antibacterial-and-antifungal-drugs-guidance-industry
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/antibacterial-therapies-patients-unmet-medical-need-treatment-serious-bacterial-diseases
Public meeting: https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/fda-public-meeting-limited-population-pathway-antibacterial-and-antifungal-drugs-07122019

Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD)

- Seeking approval under the LPAD pathway does NOT preclude seeking other designations (fast track, breakthrough therapy, priority review, QIDP designations or accelerated approval pathway)
- Request must be submitted with the original NDA, BLA or efficacy supplement
- Implications for patient labeling and promotional material

Developing Drugs for TB Treatment

TB Drug Development Programs

- Activity of antimycobacterial drugs can be evaluated in trials of early bactericidal activity (EBA) and/or in phase 2 trials with microbiological outcomes at early time points
- Contribution of each drug to the treatment effect should be evaluated
- Two adequate and well controlled trials are optimal

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pulmonary-tuberculosis-developing-drugs-treatment

TB Drug Development Programs

- However, at least one adequate and well controlled trial demonstrating clinically meaningful and statistically robust treatment effect in subjects with pulmonary TB may suffice
- Additionally, there must be:
  - Confirmatory evidence from nonclinical and *in vitro* studies, EBA studies and early phase trials, and
  - An adequate safety database and evidence of safety of the drug

Clinical Trial Design

- Noninferiority (NI)
  - An investigational regimen performs within a prespecified margin of performance of the standard regimen
  - A data-driven justification of the NI margin must be provided, based in part, on historical evidence of sensitivity to drug effects (HESDE)
- Superiority
  - An investigational regimen shows superior efficacy over the standard regimen
  - Investigational drug plus optimized background regimen (OBR) is compared with placebo plus OBR

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pulmonary-tuberculosis-developing-drugs-treatment

Study Population

- Adult and adolescent subjects (if possible)
- Pediatric populations should be included as early as possible
- Subjects with drug-susceptible (DS) or drug-resistant (DR) *M. tuberculosis*
- Pulmonary vs. extra-pulmonary disease
- HIV infection
- Enrichment strategies for DR TB
  - Contacts of subjects with DR TB
  - Subjects
    - In areas with high prevalence of drug resistance
    - Who relapse after previous treatment
    - With disease progression on a standard regimen

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pulmonary-tuberculosis-developing-drugs-treatment

Endpoints

- Endpoints should be well-defined and reliable
  - A clinical endpoint directly measures a therapeutic effect of a drug - an effect on how a patient **feels** (e.g., symptom relief), **functions** (e.g., improved mobility), or **survives**
  - A surrogate endpoint [Section 507 (21 U.S.C. 357(e)(9)]) is a marker (e.g., a laboratory measurement, radiographic image, physical sign, or other measure such as serology) that is not itself a direct measure of clinical benefit and is a:
    - Validated endpoint that is known to predict clinical benefit and could be used to support traditional approval of a drug or biological product, or
    - Endpoint that is reasonably likely to predict clinical benefit and could be used to support accelerated approval of a drug or biological product

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pulmonary-tuberculosis-developing-drugs-treatment

Surrogate Endpoint for TB

- Sputum culture conversion (SCC) 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), is considered as surrogate endpoint reasonably likely to predict clinical benefit
  - The time to sputum culture conversion (SCC) is the time to the first sterile culture, verified by *M. tuberculosis* culture negativity in at least two subsequent consecutive sputum specimens taken at least 7 to 14 days apart
  - Sponsors should obtain serial cultures at specific time points during treatment (e.g., every 2 weeks or every month).

Considerations for a Drug Approved Under the Accelerated Approval Pathway

- FDA requires the sponsor to "study the drug further, to verify and describe its clinical benefit" [CFR21 314.510]
  - These studies are known as Phase 4 confirmatory trials.
  - If the confirmatory trial shows that the drug actually provides a clinical benefit, then FDA grants traditional approval for the drug.
  - If the confirmatory trial does not show that the drug provides clinical benefit, FDA has regulatory procedures that could lead to removal of the drug from the market.

https://www.fda.gov/drugs/information-health-care-professionals-drugs/accelerated-approval-program
https://www.ecfr.gov/current/title-21/chapter-I/subchapter-F/part-601/subpart-E

Clinical endpoints for tuberculosis

The suggested primary clinical efficacy endpoint encompasses:

- Survival, *and*
- Evaluation of *M. tuberculosis* growth on serial sputum culture examinations at a fixed time point following randomization for all treatment arms, *and*
- A period of follow-up after completion of the planned treatment period

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pulmonary-tuberculosis-developing-drugs-treatment

Clinical Endpoints for TB (continued)

- **Clinical success**
  - Alive
  - Achieved *M. Tb* culture negativity on serial sputum samples
    - every 2 weeks or once a month during treatment and every 3 months following treatment completion
  - No relapse or recurrence

Clinical Endpoints for TB (continued)

- **Clinical failure**
  - Progression of pulmonary disease on treatment
  - Switch in therapy due to intolerance or clinical progression
  - Signs/symptoms of TB during follow-up
  - Growth of *M. Tb* on sputum culture
    - Failure to achieve culture negativity during treatment
    - Failure to maintain culture negative status after a specific time point in the trial or during follow-up
  - Death during treatment or follow-up

Safety Data

- Based on signals from nonclinical studies, appropriate safety safeguards (safety monitoring, inclusion/exclusion criteria) need to be included in clinical trials
- Hepatotoxicity and QT interval prolongation are common with TB drugs, in addition to other adverse events
- For assessment of risks and benefits in subjects with unmet medical need, a safety database of 300 subjects may suffice
  - Additional safety data may be requested, e.g., through postmarket study(ies) or enhanced pharmacovigilance

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/antibacterial-therapies-patients-unmet-medical-need-treatment-serious-bacterial-diseases

Recent Approvals of TB Drugs

- Bedaquiline (2012) – Accelerated Approval using a surrogate endpoint based on SCC

- Bedaquiline, Pretomanid, Linezolid (BPaL, 2019) – Traditional Approval based on a clinical endpoint; LPAD Pathway

Development of New Drugs/Innovative Treatment Regimens

- FDA is committed to working with industry, academia and other partners to further the development of new drugs for tuberculosis and/or innovative treatment regimens (including shortened regimens)
- Early engagement with FDA during the drug development program is encouraged
- Sponsors seeking indications for extrapulmonary tuberculosis should discuss with FDA endpoints that evaluate the extrapulmonary site(s)

FDA U.S. FOOD & DRUG ADMINISTRATION

Thank you!