Ramya Gopinath, Associate Director for Therapeutic Review, Division of Anti-infectives at FDA
Developing TB drugs: A regulatory perspective

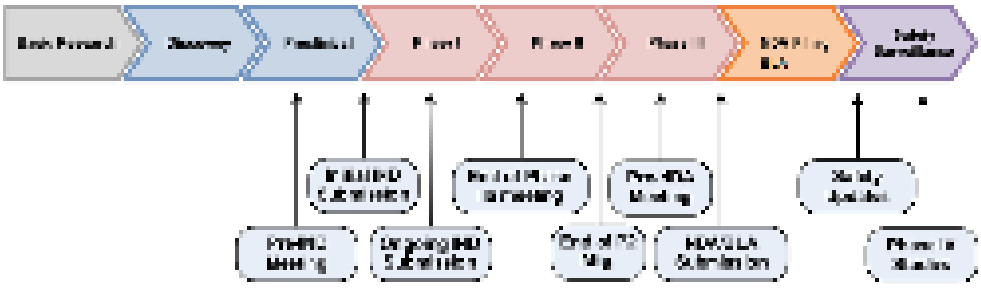
Regulatory considerations applied from LA ARV development

Publications to facilitate development of LA ARVs for HIV treatment and prevention.

- Novel challenges due to unique PK properties of ARVs (2015).
  - Appropriate dosing regimen; need for OLI; leveraging existing data from an approved oral agent.
- Key considerations for LAIs, implants, and MAPs (2020).
  - In particular, the impact of residual drug exposures following discontinuation of the LAI product and use of LA formulations in specific populations (i.e., children and pregnancy).

General drug development and specific considerations for the TB indication

Overview of the drug development pathway.



Early FDA consultation is encouraged.

Potential scenarios for LA TB drug development.

- Novel LA TB drug or LA formulation of an approved TB drug. Other scenarios exist, but will not be discussed here (e.g., prodrug).
- Two adequate and well-controlled (AWC) trials are optimal, demonstrating clinically meaningful and robust statistical therapeutic effect for PTB.
- One AWC may suffice, supported by confirmatory nonclinical and *in vitro* studies:
  - Evaluation of drug activity via early bactericidal activity (EBA) studies that quantify viable bacteria on solid or liquid media and/or P2 trials with early microbiological outcomes.
  - Goals are to inform: **Bactericidal effect** of candidate drug; **Dose selection; Preliminary safety and tolerability**; and **Contribution of each drug to the overall treatment effect**.

General features of TB treatment trials apply to long-acting and short-acting (SA) formulations.

- Noninferiority (NI) or superiority design.
  - NI trial evaluates whether the performance of an investigative regimen falls within a pre-specified margin of the standard regimen (e.g., treatment-shortening regimen or investigational drug replaces one drug in the regimen).
  - Superiority trial often evaluates the investigative drug + OBR vs placebo + OBR**.**
- Considerations for inclusion of study participants.
  - Adults and adolescents; Early pediatric development is encouraged; Pulmonary vs extra-pulmonary disease, HIV infection, and DS- or DR-TB based on trial objectives.
- Clinical endpoint directly measures the therapeutic effect of a single drug or regimen.
  - Accounts for survival, *Mtb* growth on serial sputum culture examinations, and a follow-up period.
    - Clinical success: Alive; Serial *Mtb* culture negative; No relapse or recurrence during follow-up.

        - Clinical failure: Death; *Mtb* growth on sputum culture; Disease progression on treatment; Switch in therapy due to intolerance or clinical progression; Signs/symptoms of TB during follow-up.
- Safety considerations.
    - Size of the safety database. Discussed with the sponsor during clinical trial formulation.
    - Management of AEs. Hypersensitivity, QT prolongation, and hepatotoxicity.
    - Robust safety monitoring. Informed by safety profile, if there is an approved oral formulation.
    - Risk management strategies. Strict inclusion criteria; Initial dosing in 1-2 sentinel participants; Stringent stopping rules; Safety review committee.
- Surrogate endpoint: A marker that is not a direct measure of clinical benefit.
    - Validated endpoint known to predict clinical benefit could support traditional approval (e.g., HIV viral load in HIV treatment trials).
    - An endpoint reasonably likely to predict clinical benefit could support accelerated approval. (e.g., Positive to negative sputum culture conversion during TB treatment using time-to-conversion analysis or a fixed timepoint).
- Clinical pharmacology considerations for LA TB drug formulations.
    - Dosage form is key (Injectable vs MAP vs implant).
    - Identification of an appropriate dosing regimen (e.g., Injection volume, location, and number).
    - Impact of missed doses (Forgiveness of the regimen; Role of existing oral agent?) and residual systemic exposure after treatment completion (Resistance and potential AEs).

Drug applications for a LA formulation of an approved TB drug

Application type should be discussed with the FDA early in development – the distinction is not always clear.

- A broad distinction is the source of data for safety and effectiveness.
    - 505(b)(1): Safety and efficacy studies are conducted by or for the drug sponsor.
    - 505(b)(2): At least some of the evidence is from studies not conducted by the applicant, and applicant has not obtained a right of reference or use.
- Potential 505(b)(2) scenarios include changes in:
    - **Dosage form** (e.g., Solid oral to transdermal MAP).
    - **Formulation** (e.g., Different quantity or quality of excipients than approved drug).
    - **Combination product** (e.g., New combination of previously, individually approved AIs).
    - Strength; Route of administration; Substitution of a different AI (Approved or unapproved); Dosing regimen; Active ingredient; or Indication.

Additional development considerations.

- Leverage exposure-response relationships from SA formulations.
- Role of the SA formulation as an oral lead-in (Quickly achieve steady state or evaluate safety) or supplement given in concert (Cover potential missed doses).

Regulatory pathways and designations to facilitate LA TB drug development

Accelerated approval.

- Approval is based on a surrogate endpoint or clinical endpoint that can be measured earlier than morbidity or mortality (Traditional approval is based on a clinical endpoint or validated surrogate endpoint).
- ***Trial to confirm clinical benefit must be ongoing at the time of approval.***

Expedited programs.

- Designed to address unmet medical need in the treatment of serious or life-threatening conditions (i.e., TB).
- Fast Track designation; Breakthrough Therapy designation; Priority Review.
- Qualified infectious disease product designation; Limited population pathway for antibacterial and antifungal drugs (LPAD).