Antimycobacterial Drug Development

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Antimycobacterial Drug Development

• Need for new therapies to treat patients both now and in the future

• Global burden of disease from TB (WHO 2011 estimates)*
  – 8.7 million new cases of TB (13% co-infected with HIV) (2011)
  – 1.4 million people died from TB, including almost one million deaths among HIV-negative individuals and 430,000 among people who were HIV-positive.

• Development of resistance erodes our therapeutic armamentarium

• Ideally -- shorter regimens, better tolerated, high efficacy, new mechanisms of action/preserved activity in setting of resistance to other drugs, fewer drug interactions...

* Source: WHO: *Global tuberculosis 2012*
Outline

• Antimycobacterial Drug Development
  – Early phase development
  – Traditional and accelerated approval

• FDA information resources on the web

• EMA-FDA parallel scientific advice

• GAIN

• Tropical Disease Priority Review Vouchers
Early Phase Development

- Preclinical data
- In vitro activity data / mechanism of action
- Data from animal models of infection
- Phase I - safety / tolerability / pharmacokinetics
- Early bactericidal activity studies
  - 7 to 14 days in treatment naïve, immunocompetent, low risk for resistance and extrapulmonary disease
- Phase 2 studies with microbiological outcomes
  - microbiologic endpoint at 8 weeks in combination with other drugs
- Provides a rational means to explore the investigational drug’s activity and use in a regimen prior to embarking on phase 3
Traditional and Accelerated Approval

• Traditional full approval
• Accelerated approval (21 CFR 314.500)
  – certain new drugs for serious or life-threatening illnesses
  – 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
  – Demonstration of efficacy that relies upon a surrogate endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity
  – Example: Clinical trials for Sirturo (bedaquiline)
  – June 3, 2009: Anti-Infective Drugs Advisory Committee Meeting
Accelerated Approval

- Accelerated Approval drugs subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.
- Postmarketing studies would usually be studies already underway.
- When required to be conducted, such studies must also be adequate and well-controlled.
- The applicant shall carry out any such studies with due diligence.
Phase 3 Clinical Trial Designs-1

Trial designs to demonstrate superiority

- test drug + background regimen (BR) ≥ placebo + BR

- a regimen of one or more investigational drugs is compared to a standard regimen, with efficacy demonstrated by showing superiority of the investigational regimen over the standard regimen*

*See the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination.*
Phase 3 Clinical Trial Designs-2

Trial designs to demonstrate noninferiority

- Test + ABC non-inferior to D + ABC
  - The investigational drug treatment group is within an acceptable noninferiority margin based on the known quantitative and reliable contribution within the standard regimen of the drug (D) that has been replaced.

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

Std + Test 4 months vs. Std 6 months

![Bar graph showing cure rate comparison between Std + Test 4 months and Std 6 months. The bar for Std + Test 4 months is darker blue, indicating a higher cure rate, while the bar for Std 6 months is red, indicating a lower cure rate.](image-url)
A Treatment Shortening Example

Std + Test 4 months vs. Std 6 months

Cure rate

Treatment regimen

Std + Test 4 mo

Std. 6 mo

Std. 4 mo

Historical info

July 30, 2009 FDA public workshop: Issues in the Design of Clinical Trials of Antimycobacterial Drugs for Treatment of Tuberculosis; Public Workshop

http://www.fda.gov/Drugs/NewsEvents/ucm168975.htm
Phase 3 Clinical Trial Designs-3

• Appropriate design for phase 3 clinical trials depends on a number of factors
• Properties of the investigational drug or regimen under study
  – Mechanism of action / effect of current mechanisms of resistance
  – Early safety assessments / preclinical findings
• Patient population(s) that are eligible for the trial
  – Risk / Benefit in the proposed population of use
• With advances in the field, population(s) studied, trial design options may change
• Essential that there always be clear pathways for studying new drugs for treatment of tuberculosis
• Evidence document* describes reliance upon a single phase 3 trial with supportive evidence

*Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. 1998
Phase 3 Clinical Trial Design-4

- **Endpoint (pulmonary tuberculosis)**
  - Alive, sputum culture negative & no relapse/recurrence

- **Surrogate endpoint (accelerated approval)**
  - Sputum culture conversion
  - Follow with results from a confirmatory trial

- **Safety database**
  - Recommend approx. 500 at dose and duration
    - in setting of unmet need approx. 300 if benefit risk supports
  - Challenges of concomitant medications and comorbidities – control group can be valuable in interpreting data
• Guidance documents

• Advisory committee webpage
  – http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/default.htm
Resources - 2

• Publicly available FDA review documents

• Product labeling
EMEA-FDA Parallel Scientific Advice

The European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA) have agreed to exchange views on scientific issues during the development phase of new medicinal products (i.e., new human drugs and biologics). The EMEA and the FDA have agreed to the following principles regarding these meetings. Both EMEA and FDA agree that making this “General Principles” statement public the websites of both agencies will make the program procedures and goals more transparent and will help answer many questions about the program that may exist in the general public. Each agency will post this statement on its website in accord with its own procedures for posting such documents.

1. These parallel scientific advice procedures usually occur at the request of the sponsor, but, in special...
GAIN

• Provides for a 5-year exclusivity extension upon approval for certain qualifying antibacterial or antifungal drugs

• Defines a Qualifying Infectious Disease Product (QIDP) as an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections, including those caused by...

• QIDPs eligible for Fast Track and Priority Review

• 24 QIDP designations for 16 different molecular entities currently
Tropical Disease Priority Review Vouchers (PRV)

- 2 awarded to date – Coartem & Sirturo
- PRV awarded at the time of approval of certain drugs for the treatment or prevention of a listed tropical disease
  - a new chemical entity
  - qualifies for a priority review
  - TB is one of the 16 listed tropical diseases

- Draft Guidance for Industry: Tropical Disease Priority Review Vouchers*

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• Thank you
Treatment regimen

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