Regulatory Aspects of Drug Development for Nontuberculous Mycobacteria Pulmonary Infections

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Disclosure

The views expressed in this presentation are those of the author and do not necessarily represent the views of the U.S. Food and Drug Administration.

Outline

- Introduction
- Regulatory standards for drug approval
- Challenges to development of drugs for non-tuberculous mycobacteria (NTM) pulmonary infections
- Possible regulatory approaches to facilitate approval of drugs for NTM pulmonary infections

Introduction

- Prevalence of NTM lung infections is increasing in the US.
- Treatment involves multi-drug regimens given for > 1 year and is associated with significant toxicity
- No drugs are FDA-approved for NTM infections
- FDA is trying to facilitate the development of drugs for treatment of NTM infections.
  - Non-Tuberculous Mycobacterial (NTM) Lung Infection Public Meeting was sponsored by FDA in October 15, 2015.

Regulatory Standards for Drug Approval

- Federal Food, Drug, and Cosmetic Act (FD&C) requires substantial evidence of a drug effectiveness from adequate and well-controlled investigations for the drug approval.
- The purpose is to distinguish the effect of a drug from spontaneous change in the course of the disease, placebo effect, or biased observation.
- Types of controls (21 CFR 314.126):
  - Placebo concurrent control
  - Dose-comparison concurrent control
  - No treatment concurrent control
  - Active treatment concurrent control
  - Historical control
- Data from one adequate and well-controlled clinical investigation and confirmatory evidence may establish effectiveness (FDAMA 1997).

Assessment of Outcomes in Clinical Trials (Terms and Definitions)

- **Clinical outcome**: An outcome that reflects how an individual feels, functions or survives.
- **Biomarker**: A characteristic (e.g., laboratory or radiographic) that measures responses to therapeutic interventions. It is not an assessment of how an individual feels, functions, or survives.
- **Endpoint**: A precisely defined variable intended to reflect an outcome of interest that is analyzed to address a particular research question.
- **Surrogate endpoint**: a substitute (e.g., a biomarker) for a direct measure of how a patient feels, functions, or survives, which is expected to predict a clinical benefit.

BEST (Biomarkers, EndpointS, and other Tools) Resource. FDA-NIH Biomarker Working Group. https://www.ncbi.nlm.nih.gov/books/NBK326791/pdf/Bookshelf_NBK326791.pdf

Regulatory Mechanisms for Drug Approval

- **Standard approval**
  - based on an endpoint measuring how a patient feels, functions, or survives
- **Accelerated approval**
  - 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
  - postmarketing confirmatory trials may be required to verify the predicted clinical benefit

FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

Challenges to Designing Trials in NTM Pulmonary Infections

- Clinical outcomes are difficult to assess due to symptoms related to underlying comorbidities (bronchiectasis, COPD, cystic fibrosis).
- Response to study drugs may vary by NTM species and underlying lung disease.
- Trials are lengthy, include multiple visits which raises issues with compliance and lost to follow-up.

Clinical Outcome Assessment in Trials in NTM Pulmonary Infections

- **Clinician reported outcome**: clinical assessment can be confounded by the progression or exacerbation of underlying diseases such as bronchiectasis, CF, or COPD.
- **Performance outcome measures**: a 6-minute walk test (6WT) has been used in pulmonary NTM clinical trials[1] and may be included as a part of clinical assessment. Additional discussion of a clinically important difference in 6WT in NTM patients is needed.
- **Patient reported outcome measures**: an important aspect of clinical outcome assessment but may be confounded by underlying comorbidities and, in case of inhaled products, by respiratory adverse events. [1]
- Overall, it may be challenging to define an endpoint in NTM pulmonary infection trials that is based on clinical assessment.

[1] Olivier KN et al. Am J Respir Crit Care Med. 2017 Mar 15; 195(6):814-823

Potential Endpoints in Trials in NTM Pulmonary Infections

Microbiological assessment

- **Culture conversion**
  - May be defined as 3 consecutive negative respiratory cultures measured at defined post-randomization time points although the number of negative cultures needed is not firmly established
  - Correlation with clinical outcome needs to be established
  - May expedite clinical program but a longer follow-up (e.g., a 12-month) may still be needed
- **12 months of culture-negative sputum**
  - Recommended treatment goal for MAC and *M. kansasii* infections [1]
  - Culture conversion may reasonably well predict sustained microbiological response so a 12-months of negative culture endpoint may not be necessary.

Radiographic assessment - may be difficult because of limited potential for improvement of MAC-related radiological abnormalities.

[1] An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases http://www.atsjournals.org/doi/full/10.1164/rccm.200604-571ST#readcube-epdf

Possible Designs of Comparative Trials for NTM Pulmonary Infections

- Superiority to demonstrate a greater response rate, shorter duration of therapy, decreased toxicity.
  - New drug combination vs. placebo (when delay in treatment is acceptable)
  - New drug combination vs. standard of care
  - A study drug + background regimen (BR) vs. BR alone
  - New drug combination vs. historical control
- Non-inferiority
  - Justification of a non-inferiority margin may be challenging

Possible Regulatory Approaches to Facilitate NTM Drug Approval

- Use of earlier surrogate endpoints, e.g., sputum culture conversion
- Potential use of a smaller clinical data package
- Contribution of individual components in a drug combination may be supported by in vitro and animal data
- The Division is happy to meet with sponsors early in drug development to discuss clinical trial design

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