Regulatory Perspective for Inhaled Antifungal Products

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Addressing Challenges in Inhaled Antifungal Drug Development
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Background

- Recent interest in inhaled antifungal products
  - Allergic bronchopulmonary aspergillosis (ABPA)
  - Invasive pulmonary aspergillosis (IPA)
- No approved inhaled antifungal products
- General principles for development of inhaled antifungal drugs similar to those for inhaled antibacterial drugs

Statutory Standards

- Substantial evidence as “evidence consisting of adequate and well-controlled investigations, including clinical investigations,…” (FD&C Act)
  - Characteristics of investigations are outlined in 21 CFR 314.126(b)
- Section 115(a) of the Modernization Act clarified that the Agency may consider “data from one adequate and well-controlled clinical investigation and confirmatory evidence” to constitute substantial evidence
  - Evidence from nonclinical and in vitro studies or another indication

Guidance on Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products

Regulatory Pathways

- Traditional 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; [21 CFR 314.500, (Subpart H)]

21 CFR part 314, subpart H; 21 CFR part 601, subpart E ; Section 506(c) of the FD&C Act as amended by section 901 of FDASIA
FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014.
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

Endpoints

- Commonly used endpoints in antifungal trials have included all-cause mortality and clinical success at a fixed time point (6-12 weeks)
- The methods of assessment of subjects' response 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 is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is likely to predict clinical benefit, but is not itself a measure of clinical benefit

21 CFR 314.126(b)(6)

Inhaled Antibacterial Drug Trials: Challenges

- Patient population: often very heterogeneous with regard to severity of illness, underlying patient characteristics and microbiologic etiology
- Endpoints: defining a clinically meaningful endpoint has been difficult; unlike acute infections, persistent symptoms related to underlying clinical condition are common. Microbiologic endpoints do not necessarily correlate with clinical outcomes
- Treatment regimens: cyclical on/off therapy has generally been used in non-cystic fibrosis bronchiectasis (NCFB), similar to the approach for cystic fibrosis (CF); unclear if other approaches might be better

Inhaled Antibacterial Drug Trials: Challenges

- Duration of Study: Optimal duration of therapy and length of follow up to determine treatment benefit is not clear
- Impact on microbiologic flora due to long-term exposure to antibacterial drugs; development of resistance and replacement with other microorganisms remain a concern
- References
  - Antimicrobial Drugs Advisory Committee meetings: November 16, 2017: Ciprofloxacin inhalation powder for NCFB; January 11, 2018: Ciprofloxacin dispersion for inhalation for NCFB; August 7, 2018: Amikacin liposome inhalation suspension for nontuberculous mycobacterial (NTM) lung disease
  - Workshops: June 27, 2018: Development of Inhaled Antibacterial Treatments for CF and NCFB; April 8, 2019: Development of Antibacterial Drugs for the Treatment of NTM Disease

Inhaled Antifungal Therapies

- Important lessons learned from inhaled antibacterial therapies for non-CF bronchiectasis and NTM lung disease
- Important to select a clinically meaningful endpoint and not one based solely on a biomarker or laboratory test
- Adequate development work, including phase 2 trials, will be helpful in determining key design elements of future trials
- Heterogeneity in patient population should be considered; variability in treatment effect can affect trial results
- Collaboration with experts in Division of Pulmonary, Allergy, and Critical Care

Antifungal drugs for treatment of ABPA

- No FDA-approved drugs
- Infectious Diseases Society of America (IDSA) guidelines
  - Primary: itraconazole
  - Alternative: voriconazole, posaconazole
  - Inhaled amphotericin B mentioned for patients who fail or are intolerant to itraconazole

ABPA: Trial Issues

- Intended use of product
  - To replace oral itraconazole use, permit reduction of oral steroids, induce remission, or serve as adjunct therapy
- Patient population (underlying conditions, diagnosis and staging)
- Identification of appropriate regimen
- Use of adjunctive therapies (e.g., corticosteroids); possible confounding of efficacy assessments with weaning of steroids

ABPA: Trial Issues

- Endpoints (measures of lung function; patient-reported outcome (PRO) measures; number, severity of exacerbations; time to event)
  - Must be clinically meaningful, not solely based on biomarker or laboratory test
- Exacerbations
  - Definition of beginning and end of an event
  - Events due to asthma or other underlying condition vs. ABPA
- Microbiologic assessments when goal is reduction of burden rather than eradication
- Duration of trials

Drugs for treatment of IPA

- FDA-approved
  - Azoles: voriconazole, itraconazole, isavuconazonium sulfate; posaconazole (prophylaxis of invasive infection only)
  - Caspofungin (refractory to or intolerant of other therapies)
  - Amphotericin B formulations
- IDSA guidelines
  - Primary: voriconazole
  - Alternative: liposomal amphotericin B, isavuconazonium sulfate
  - Salvage: various
  - Inhaled AmB for tracheobronchial aspergillosis associated with ischemic injury in lung transplant patients; consider inhaled AmB for antifungal prophylaxis in lung transplantation

Inhaled Therapies for IPA: Trial Issues

- Intended use
  - Prophylaxis vs. treatment
  - Adjunct to systemic therapy vs. monotherapy
  - Implications for trial design: endpoints; superiority vs. noninferiority
- Target population
  - Hematologic malignancy, lung transplantation, ICU, COPD
- Endpoints for subpopulations under study
  - Clinical, microbiologic, radiologic, PRO
  - Assessment of response to therapy

Other Important Considerations

- Device issues should be addressed early in development; the Division seeks input from:
  - The Center for Devices and Radiological Health for device-specific issues
  - The Division of Medication Error Prevention and Analysis for issues related to human factors
  - Patient Labeling Team in the Office of Medical Policy for review of Instructions for Use (IFU)
- Chemistry, Manufacturing, and Controls (CMC):
  - Early interactions to discuss issues related to CMC (e.g., PIND/EOP2, pre-NDA meetings)

Summary

- We recognize the need for development of safe and effective antifungal products to treat ABPA and IPA
- Trials must be feasible and interpretable (i.e., adequate and well-controlled) with clinically meaningful endpoints
- We recommend phase 2 trials to evaluate possible endpoints, assess treatment effects, and determine other important design elements for future trials
- We will continue to work with Sponsors on trial development and appropriate data packages to support approval


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