

Regulatory Considerations for Antifungal Drug Development

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Background

- There is renewed interest in antifungal drug development
 - Candidiasis, less common molds, coccidioidomycosis, unmet need population (refractory disease, resistance, treatment intolerant)
- While this is encouraging, we recognize that there are scientific and practical challenges that need to be addressed
 - Today's workshop will help provide some solutions and also identify some key areas that will need further discussion
- We also recognize the economic challenges with anti-infective drug development

Background

- General principles for antifungal drug development are similar in several aspects to those for antibacterial drug development
- We have made significant progress with antibacterial drug development and have clearly-defined and scientifically sound approaches that are feasible for many clinical conditions
 - This was achieved by engagement with stakeholders, public-private partnerships and regulatory flexibility supported by scientific evidence
 - Important lessons were learned from completed programs-dose selection, importance of the body site of infection, animal models
 - There is more work to be done, such as refining/use of novel endpoints, trial designs for difficult to study indications, special populations

Regulatory Pathways

- Traditional approval
 - Generally 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)]
 - Must meet the same statutory standards for safety and effectiveness as traditional approval

Data Package

- Statutory Standard: Substantial evidence consisting of adequate and well-controlled investigations
- At least one adequate and well-conducted trial per indication
 - supportive evidence from nonclinical and in vitro studies or another indication
- For products with orphan designation, the statutory standard needs to be met; effectiveness demonstrated in adequate and well controlled investigation(s)
- Recent trials for aspergillosis, candidemia/invasive candidiasis have used noninferiority (NI) trial design; large treatment effect; appropriate justification of the NI margin

Endpoints

- Commonly used endpoints in antifungal trials have included all-cause mortality and clinical success at a fixed time point
- Endpoints selected 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

Role of Diagnostics

- For candidemia/invasive candidiasis trials, we have allowed use of non-culture-based tests for enrollment
- Galactomannan test has been used in IA trials for patient identification and definition of patient populations
- Important that the tests adequately detect the disease of interest; especially important in NI trials to ensure that the population studied has the disease of interest
- In general, diagnostic tests do not have to be FDA-cleared or FDA-approved for use in a clinical trial if being used for enrichment purposes
- Qualification of an endpoint is not a pre-requisite for use in clinical trials

Safety

- Based on signals from nonclinical studies, appropriate safeguards (monitoring, trial population) need to be included in the clinical trials
- Safety database at the proposed dose and duration likely to be small (~300 patients); additional data may be needed if there is a safety signal
- There might be a need for additional safety data, e.g., through postmarketing requirements or enhanced pharmacovigilance

Some Considerations Moving Forward

- Data packages that are feasible and provide interpretable data, particularly for the more difficult to study fungal infections
- How best to leverage data from nonclinical studies to support the small data packages
- Role of external controls, particularly for certain types of fungal infections
- Developing oral step-down therapies
- Developing products for the pediatric population, including neonatal infections
- Developing inhaled antifungal therapies
- Developing therapies for prophylaxis of invasive fungal infections

QIDP Designation

- Antibacterial or antifungal human drug that is intended to treat serious or life-threatening infections
- Provides for the following incentives
 - Additional 5 years marketing exclusivity for certain drugs
 - Priority review for the first application for a QIDP
 - Eligible for fast track designation
- Designation can be requested at any time before submission of the marketing application
- Over 200 antibacterial/antifungal products have QIDP designation; 26 designated products have been approved

Tropical Disease Priority Review Voucher

- Applications for products to prevent or treat diseases listed under Section 524 of the FD&C Act may qualify for a Tropical Disease Priority Review Voucher (PRV) if they:
 - for prevention or treatment of a disease on the “tropical disease list”
 - otherwise qualify for priority review
 - contain no active ingredient (including any salt or ester of an active ingredient) that has been approved in any other application under section 505(b)(1) of the FD&C Act or section 351 of the PHSA
 - contain reports of one or more new clinical investigations (other than bioavailability studies) that are essential to the approval of the application and conducted or sponsored by the sponsor, **and**
 - provide in the application an attestation that such report(s) were not submitted as part of an application for marketing approval or licensure by certain regulatory authorities prior to September 27, 2007
- A PRV can be used to obtain priority review designation for a subsequent application that does not itself qualify for priority review as described in the guidance

Additions to List of PRV-Eligible Diseases

- Section 524 allows FDA to add by order “any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations” to the list of diseases eligible for Tropical Disease PRV consideration
- Interested parties may submit additional diseases with supporting materials for designation to the public docket FDA-2008-N-0567-0011, which FDA reviews on a rolling basis
(<https://www.regulations.gov/document?D=FDA-2008-N-0567-0011>)
- Cryptococcal meningitis was added to the list of eligible diseases and a decision was made not to designate coccidioidomycosis

<https://www.fda.gov/about-fda/center-drug-evaluation-and-research/tropical-disease-priority-review-voucher-program>

<https://www.federalregister.gov/documents/2020/07/15/2020-15255/notice-of-decision-not-to-designate-coccidioidomycosis-as-an-addition-to-the-current-list-of>

LPAD Pathway

- Based on a benefit-risk assessment that more flexibly takes into account the *severity, rarity, or prevalence* of the infection the drug is intended to treat and the lack of alternatives available for the patient population.
- Requirements
 - The drug is intended to treat a *serious or life-threatening infection* in a *limited population* of patients with *unmet needs*
 - Standards for approval under 505(c) and (d) or standards for licensure under 351 of Public Health Service Act are met (i.e., substantial evidence of effectiveness provided)
 - Written request from the Sponsor that the drug be approved as a limited population drug

LPAD Pathway: Conditions for Approval

- Labeling: To indicate that safety and effectiveness has only been demonstrated with respect to a limited population
 - All advertising and labeling will include “Limited Population” in a prominent manner, and
 - The prescribing information will contain the statement “This drug is indicated for use in a limited and specific population of patients”
- Promotional Materials:
 - Pre-submission of promotional materials at least 30 days prior to dissemination of such materials

Experience with the LPAD Pathway

- Two NDAs have been approved under the LPAD pathway
 - Arikayce
 - Pretomanid
- The approved patient population for each product is limited, specific, and well-defined
- Treatment effect was demonstrated in an adequate and well controlled trial for each product
- Benefit-risk profile of the products was considered acceptable in the indicated limited population of patients who have few/no treatment options
- Limitations of the data are reflected in product labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ARIKAYCE safely and effectively. See full prescribing information for ARIKAYCE.

ARIKAYCE® (amikacin liposome inhalation suspension), for oral inhalation use

Initial U.S. Approval: 2018

LIMITED POPULATION

WARNING: RISK OF INCREASED RESPIRATORY ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

ARIKAYCE has been associated with a risk of increased respiratory adverse reactions, including, hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases. (5.1, 5.2, 5.3, 5.4)

INDICATIONS AND USAGE

LIMITED POPULATION: ARIKAYCE is an aminoglycoside antibacterial indicated in adults who have limited or no alternative treatment options, for the treatment of *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. As only limited clinical safety and effectiveness data for ARIKAYCE are currently available, reserve ARIKAYCE for use in adults who have limited or no alternative treatment options. This drug is indicated for use in a limited and specific population of patients. (1)

This indication is approved under accelerated approval based on achieving sputum culture conversion (defined as 3 consecutive negative monthly sputum cultures) by Month 6. Clinical benefit has not yet been established. (1)

Limitation of Use:

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PRETOMANID TABLETS safely and effectively. See full prescribing information for PRETOMANID TABLETS.

PRETOMANID tablets, for oral use

Initial U.S. Approval: 2019

LIMITED POPULATION

INDICATIONS AND USAGE

Limited Population: Pretomanid Tablet is an antimycobacterial indicated, as part of a combination regimen with bedaquiline and linezolid for the treatment of adults with pulmonary extensively drug resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB). Approval of this indication is based on limited clinical safety and efficacy data. This drug is indicated for use in a limited and specific population of patients. (1)

Limitations of Use (1):

- Pretomanid Tablets are not indicated for patients with:
 - Drug-sensitive (DS) tuberculosis
 - Latent infection due to *Mycobacterium tuberculosis*
 - Extra-pulmonary infection due to *Mycobacterium tuberculosis*
 - MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy
- Safety and effectiveness of Pretomanid Tablets have not been established for its use in combination with drugs other than bedaquiline and linezolid as part of the recommended dosing regimen.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207356s000lbl.pdf

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212862s000lbl.pdf

Pediatrics

- Under the Pediatric Research Equity Act (PREA), pediatric studies are required unless requirement is waived, deferred, or not applicable
- Although antifungal products with orphan designation are exempt, we encourage Sponsors to consider developing products for children
 - need safe and effective therapies for this population
 - can extrapolate efficacy from adults for many fungal infections
 - we are willing to consider issuing a pediatric written request, if there is interest
- Recently issued guidance on anti-infective drug development for pediatric population

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-anti-infective-drug-products-pediatric-population>
<https://www.fda.gov/drugs/development-resources/written-requests-issued>

Summary

- Provided a high-level overview of the key considerations for antifungal drug development and reviewed some incentives and pathways that are relevant to antifungal drug development
- We recognize the unmet need and the practical challenges in developing antifungal drugs
- Important for all of us to work together to find feasible and scientifically sound solutions to address patient needs
- There are many important lessons learned with antibacterial drug development that are relevant to and can guide further discussions on antifungal drug development

Thanks!

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