Regulatory and Clinical Trial Considerations for Drug Development for Coccidioidomycosis

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Valley Fever Workshop
August 5, 2020

Background

- FDA has seen some renewed interest in antifungal drug development for coccidioidomycosis and other invasive fungal diseases
- General principles for antifungal drug development are similar in several aspects to those for antibacterial drug development
- Discuss some aspects of antifungal drug development from a regulatory perspective; focus on systemic fungal disease
  - Regulatory approaches
  - Incentives
  - NDA data packages
  - Clinical trial design considerations

Drugs for Treatment of Coccidioidomycosis

- FDA-approved: Ketoconazole, Amphotericin B deoxycholate
- Standard of care (not FDA-approved): Fluconazole, itraconazole
- Other (not FDA-approved): Voriconazole, posaconazole, etc.
- Investigational drugs in human studies/animal models e.g., VT-1598, NikkomycinZ, Olorofim, APX-001 (*see weblinks in references slide)*
- No approved new drug application (NDA) in > 20 years

Regulatory Pathways

- Traditional approval
  - Generally based on a clinical 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)]
- Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD)
  - For drugs that are intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs
    - Examples: Pretomanid and Arikayce (liposomal amikacin inhalation suspension) were approved under the LPAD pathway

https://www.fda.gov/drugs/development-resources/limited-population-pathway-antibacterial-and-antifungal-drugs-lpad-pathway
FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014.
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

Accelerated Approval

- A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit
- Must meet the same statutory standards for safety and effectiveness as traditional approval
- The accelerated approval pathway has been used primarily in settings in which the disease course is long and an extended period of time would be required to measure the intended clinical benefit of a drug; less of a role in acute infectious diseases
- For drugs granted accelerated approval, postmarketing confirmatory trials have been required to verify and describe the anticipated clinical benefit

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
https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

QIDP Designation

- Products being developed for treatment of coccidioidomycosis may be eligible for Qualified Infectious Disease Product (QIDP) designation
- Designation can be requested at any time before submission of the new drug application
- Provides for the following incentives
  - Additional 5 years marketing exclusivity for certain drugs
  - Priority review for the first application for a QIDP
    - Priority review timeline is within 6 months (compared with 10 months under standard review).
- Eligible for Fast Track designation

GAIN Provision (Title VIII of FDASIA under section 505E of the FD&C Act):
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM594213.pdf

Fast Track Designation

- *". . . if it is intended, whether alone or in combination…, for the treatment of a serious or life-threatening disease.., and it demonstrates the potential to address unmet medical needs for such a disease or condition*"

- Information to support designation will depend on the stage of drug development
  - Evidence of activity in a nonclinical model, a mechanistic rationale, or pharmacologic data
  - Available clinical data

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

Fast Track Designation

- Allows for frequent interactions with the review team including pre-IND meetings, end-of-phase 1 meetings, and end-of-phase 2 meetings
- Allows for submission and review of portions of a new drug application (rolling review)
- Designation may be rescinded if it no longer meets the qualifying criteria

Breakthrough Therapy Designation

- Clinical evidence must show that the drug may demonstrate substantial improvement over available therapy on one or more clinically significant endpoints
- Intensive guidance on the drug development program, beginning as early as Phase 1
- Organizational commitment involving senior management
- Eligible for rolling review
- Could be eligible for priority review if supported by clinical data at the time of BLA/NDA/efficacy supplement submission
- All benefits of Fast-Track Designation

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

Data Package for NDA

- When seeking an indication for coccidioidomycosis
  - At least one adequately controlled trial with supportive evidence from a clinical trial in another indication and/or nonclinical and *in vitro* studies

- For products with orphan designation, the statutory standard needs to be met; effectiveness demonstrated in adequate and well controlled investigation(s)

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207500Orig1207501Orig1s000TOC.cfm

Nonclinical Data - Evidence

- Activity of antifungal drug *in vitro* and *in vivo*
  - *C. immitis, C. posadasii*
- Animal Model - Experimental design considerations
  - Choice of animal species – based on natural history of disease in animal similar to humans; the intended clinical use
  - *Coccidioides* species and strain(s)
  - Inoculum concentration and route of infection
  - Trigger-to-treat / time of initiation of treatment
  - Route of treatment
  - Endpoints
    - Mortality
    - Changes in CFU in the target organ e.g., brain and lungs
    - Serological and/or molecular testing
    - Histopathology, Radiology
  - Appropriate controls

PK-PD Assessments - Animal Model

- There is no preferred animal model(s) of coccidioidomycosis to assess antifungal activity or for pharmacokinetic-pharmacodynamic (PK-PD) assessments
- Consideration should be given to target infection site while selecting an animal infection model(s)
- PK-PD assessments from an animal infection model have potential to:
  - Aid in selecting a dosing regimen for clinical trials
  - Characterize and compare drug's activity from clinically relevant exposure at target infection site
  - Provide supportive evidence for drug's activity

Clinical Trials

- Trial Designs
  - Noninferiority (NI)
    - Must be able to provide a data driven justification of the NI margin
    - A drug recognized as current standard of care is acceptable as an active comparator
    - Recent trials for invasive fungal disease have used NI trial design
  - Superiority
    - Placebo (if clinically acceptable)
    - Active control
    - External/Historical control – needed to interpret a single-arm trial

Endpoints

- Endpoints 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 such as serology, that is likely to predict clinical benefit, but is not itself a measure of clinical benefit 21 CFR 314.126(b)(6)
- Clinical endpoints for Coccidioidomycosis
  - Will depend on spectrum of clinical presentations (localized vs. disseminated disease), characteristics of patient population
  - May include a patient reported outcome (PRO) measure
  - Cocci scoring system (CCS) has been used in published clinical trials
  - If a biomarker of disease is proposed, for example, a serological marker, *Coccidioides* DNA by PCR, it should be reasonably likely to predict clinical benefit

Endpoint - Patient Reported Outcomes

- Definition: A measurement based on a report that comes directly from the patient about the status of the patient's health condition without interpretation of the patient's response by a clinician or anyone else.
- Can be useful for clinical outcome assessment for chronic disease/infections.
  - Utility as clinical outcome assessment in coccidioidomycosis trials?
- FDA PRO Guidance* describes measurement principles applicable to all types of Clinical Outcome Assessments

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf

Role of Diagnostics

- Important that the test(s) adequately detects the disease of interest; especially important in NI trials to ensure that the population studied has the disease of interest
  - e.g., Galactomannan test has been used in IA trials for patient identification and definition of patient populations, https://www.fda.gov/media/94480/download
- 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
- If the diagnostic tests are not FDA-cleared, then information supporting the intended context of use should be provided
- Qualification of a diagnostic as an endpoint is not a pre-requisite for use in clinical trials; CDER Biomarker Qualification Program helps to develop biomarkers as drug development tools

https://www.fda.gov/drugs/drug-development-tool-qualification-programs/cder-biomarker-qualification-program

Safety Data

- Based on signals from nonclinical studies, appropriate safety safeguards (safety monitoring, inclusion/exclusion criteria) need to be included in clinical trials
- Safety database at the proposed dose and duration is likely to be small in coccidioidomycosis trials; therefore, additional safety data may be needed if there is a safety signal
- Additional safety data may be requested, e.g., through postmarket study(ies) or enhanced pharmacovigilance

Summary

- Provided a high-level review of some key considerations for drug development for coccidioidomycosis
  - Regulatory pathways and incentives relevant to drug development
  - Trial designs, endpoints, diagnostics
- We encourage sponsors to engage in early discussions with the Division of Anti-Infectives

References: Weblinks for Investigational Drugs

Nonclinical studies:

- Olorofim: https://pubmed.ncbi.nlm.nih.gov/29941638/
- VT-1598: https://pubmed.ncbi.nlm.nih.gov/29437615/
- NikkomycinZ: https://pubmed.ncbi.nlm.nih.gov/23488972/
- APX-001: https://pubmed.ncbi.nlm.nih.gov/30455238/

Clinical studies:

- VT-1598: https://clinicaltrials.gov/ct2/show/NCT04208321?type=Intr&cond=Coccidioidomycosis&draw=2&rank=8
- NikkomycinZ: https://clinicaltrials.gov/ct2/show/NCT00834184?term=nikkomycin&draw=2&rank=2
- Posaconazole: https://clinicaltrials.gov/ct2/show/NCT00423267?type=Intr&cond=Coccidioidomycosis&draw=2&rank=3

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Thank you!

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