Clinical Trials for LPAD Products:
Past Precedents & Future Scenarios

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LPAD Pathway – Limited Population

- The concept of streamlined development for antibacterial therapies in serious infections with unmet need was introduced in the Unmet Needs FDA Guidance (*August 2017*).

- The newest concept introduced in the LPAD Pathway FDA Guidance (*June 2018*) is “limited population”
  - A limited population is a group of patients that is limited in such a way that is clinically relevant to health care providers
  - A limited population may be a defined subset of a broader population of patients for whom the drug could potentially be effective or, in some cases, may be the only population of patients for whom the drug may be effective because of its narrow spectrum of activity

LPAD Pathway – Streamlined Development

- Possibilities for streamlined development:
  - A single adequate and well-controlled trial with supportive evidence of effectiveness
  - Wider non-inferiority margins than used for traditional programs
  - Nested, non-inferiority/superiority designs
  - Smaller, shorter, fewer trials (relationship to subpart H regulations?)

Are these different approaches than those currently used for new antibacterial and antifungal products being developed for populations with significant unmet medical need?

LPAD Pathway – Examples

- An antibacterial drug with a narrow spectrum of activity (e.g., active against only a single species (or a few species) within a genus), and the target pathogen or pathogens occur infrequently at any body site of infection
- An antibacterial or antifungal drug that, based on available therapy, would ONLY have a role in the therapeutic armamentarium for a select patient population with no other options.

Is LPAD predominantly useful for narrow spectrum of targeted anti-bacterials and antifungals, while novel agents with improved broad spectrum activity including activity in subpopulations with resistant infections are not optimal candidates for LPAD pathway?

LPAD Pathway – Precedents ARIKAYCE®

- Positive precedent - LIMITED POPULATION: ARIKAYCE® (amikacin liposome inhalation suspension)
  - 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
- Approval pathway and support:
  - Single Phase 3 trial using a micro endpoint (sputum culture conversion) in patients with refractory MAC lung disease with supportive Phase 2 trial
  - Benefit/risk: Lack of stat/clin improvement on clinical endpoints / higher incidence of respiratory AEs
  - Subpart H accelerated approval with post-approval commitment for a confirmatory study with a clinical endpoint (like previously approved SIRTURO® (bedaquiline fumerate) for MDRTB)

Would Arikayce® still have had a path to approval without LPAD and/or was LPAD used to impose labeling and advertising restrictions on a product that would have received Subpart H approval?

LPAD Pathway – Precedents ZEMDRI®

- Negative precedent – ZEMDRI® (plazomicin) injection
  - For the treatment of patients with complicated urinary tract infections (cUTI) including Pyelonephritis. As only limited clinical safety and efficacy data are available, reserve ZEMDRI® for use in patients who have limited or no alternative treatment options.

- Approval pathway and support:
  - Not approved for blood stream infections (BSI) due to CRE
  - Change in trial design from randomized to open label indicative of challenge in enrolling this patient population
  - Sample size, demographics/differences between treatment arms, clarity of diagnosis/infection source and non-standard statistical analysis plan may have been factors in rejection; yet CRE infections are very difficult to study
  - Positive benefit/risk in UTI did not lend sufficient support to BSI indication

LPAD Pathway – Precedents ZEMDRI®

- It is recognized FDA cannot discuss confidential information relating to Zemdri® review.

Does the concept of a limited population enable the study of resistant infections in the clinical trial setting to support development and approval of new antibacterials and antifungals?

Can FDA clarify in the context of CRE infections, what sufficient evidence of effectiveness may be provided in CRE infections in order to achieve an LPAD approval?

LPAD Pathway – Industry Perspectives

- Lack of clear precedents may be limiting industry application of the LPAD guidance

- It would be more useful if LPAD could be applied to any relevant (sub)population with significant unmet medical need
  - Examples include but not limited to CRE infections or HABP/VABP population with poorer outcomes (ventilated only).
  - Limited applicability of LPAD may result in continuing lack of data in hard to study infection types/sites where safety and efficacy data are critically needed.

LPAD Pathway – Industry Perspectives

- Clarity is needed whether LPAD indication can be granted concurrently with a non-LPAD indication in a broader population

- Additional innovative trial designs accessible through the LPAD pathway need to be established
  - Alternative control groups
  - Alternative statistical approaches
  - Microbiological surrogate endpoints
  - Body site extrapolation provided reasonable evidence of penetration
  - Greater reliance on PK/PD data