Limited Population Pathway for Antibacterial and Antifungal Drugs - draft guidance -

Industry comments (continued)

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LPAD draft guidance

- LPAD guidance welcomed
  - to make life saving drugs available
  - to support the AI R&D ecosystem

- This presentation will focus on:

  - How new development and review initiatives may be applied to LPAD

  - Post marketing removal of LPAD restrictions

How New Development and Review Initiatives may be applied to LPAD

- Smaller, shorter & fewer trials… and… different?
  - Novel clinical trial design concepts:
    - Boosting controls, and Platform trials
    - RWD vs RCT in support of guidance
    - Adaptive trial design
  - Tissue agnostic approaches: pooling pathogen data across body sites
- LPAD guidance refers specifically to “streamlined clinical development” discussed in the unmet needs for serious bacterial diseases guidance* :
  - Q&A 4: nested NI / superiority design
  - Q&A 5: Pooling across different infected body sites
  - Q&A 6: Clinical trial networks and factorial design

* Antibacterial therapies for patients with an unmet medical need for the treatment of serious bacterial diseases, Aug 2017

Important Trends

- Diagnostics and surveillance
  - Translation of genotypical information to predicted susceptibility
  - Large databases capturing prevalence and spread of resistance
- Electronic patient records
  - Linking patient risk factors, pathogen genetics, treatment details and patient outcomes
  - Artificial intelligence / Machine learning
- Clinical Trial networks
  - Facilitate informed consent, continuous data collection = evolving baseline
  - International collaborations offer faster access to larger datasets
  - Empirical testing of stewardship interventions to support formulary policies
- Blurring of RWD vs RCT paradigms

Potential novel approaches to "substantial evidence"

- "Substantial evidence of effectiveness" for MDR therapy typically =
  - Demonstrated NI in similar population
  - Anecdotal clinical evidence against the target MDR pathogen
- Alternative evidence/ setting
  - Reliance on well established PK/PD modeling (vs limited clinical data)
  - Access patients typically excluded from RCT (e.g. Compassionate Use)
  - Complementary/ alternative methods to DB RCT
    - control arm boosted with matched case controls and/or shared SOC patients
    - platform trials with continuous RWD as "contemporaneous controls"
  - Endpoint flexibility as for cancer trials*
    - including approval based on "surrogate endpoint known to predict clinical benefit"
    - Is LPAD comparable to "accelerated approval" ?
- For a drug with established safety profile, could LPAD pathway allow an sNDA based just on PK/PD?

* Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, Dec 2018

Adaptive clinical trial design

- FDA guidance on adaptive clinical trial design* has recently been updated. Useful design elements include:
  - Futility analyses
  - Sample size re-estimations
  - Adaptive enrichment
  - Dose selection strategies and changes in randomization ratio.
- Model informed analyses:
  - possibility to borrow from external information
- Relevance in a setting of “continuous data collection”:
  - Define how to add experimental agents / how to replace Standard of Care

More complex design that requires upfront discussion with FDA, but potentially resulting in more valuable information for LP

* Adaptive designs for clinical trials of drugs and biologics, Sept 2018

Tissue / infection-site agnostic approaches: CT setting vs. Intended use

- Homogeneous population to compare safety and efficacy
- E.g. cUTI
- Labeling describes “usual patho-gens in a example indications”
- Intended limited population does not always make it into the label…
- Tissue limitations are not studied !

- To disrupt a troublesome pathogen (e.g. CDC and WHO lists)
- E.g. VAP in ICU, Septicemia
- Relevant pathogens accumulated across various infected body sites
- In poorly met/ unmet needs, limited to no comparison possible, hence: “resistant pathogen study”
- Phase 2a type evidence for most relevant tissues…

A pathogen focused study, stratified by body site, or using factorial design, can pool across indications and provide very meaningful insights

LPAD labeling

- Labeling reflects FDA Risk/benefit judgement
  - intended use ≠ necessarily the studied population !
  - reflect limitations of evidence and experience

LIMITED POPULATION: MYDRUG is a *(established pharmacologic class)* indicated in adults who have limited or no alternative treatment options, for the treatment of infections caused by MDR *(specific pathogen)*.

As this indication is based on limited clinical safety and effectiveness data, comprised of (e.g.) one non-comparative efficacy study and one controlled safety study in cUTI, MYDRUG should be reserved for patients who have limited or no alternative treatment options.

- LPAD labeling could present other evidence / otherwise:
  - Having only limited RCT / clinical evidence, increases the relative importance of available (non-clinical) evidence

Post-marketing removal of LPAD restrictions

Requires sNDA/ sBLA with "additional clinical data" to support "broader indication"

1. Removal of restrictions
   - NB "broader use" may anyway be limited by stewardship considerations!
   - Would PSUR and/or RWD supporting safety in the Limited Population eventually suffice to remove the LPAD labeling requirements?
2. Approval for broader indication… based on e.g.:
   - Additional LPAD claim for another problem pathogen?
   - RWE or RCT supporting safety and efficacy in the initial LP indication?
   - Similar to accelerated approval for cancer drugs/biologics?
   - Classical sNDA for a different, broader indication/ pathogen?

In Summary

We welcome the agency's ongoing activities to implement section 3042 of the 21st Century Cures Act which established the limited population pathway for antibacterial and antifungal drugs, specifically efforts to add additional regulatory flexibility in the development on eligible novel antimicrobials through an increased reliance on animal models and PK/PD data. We would also encourage the agency to consider going beyond this and include additional regulatory flexibility such as adaptive trial designs, acceptance of a greater degree of uncertainty and more flexible patient selection criteria to further streamline the process.