Current State and Further Development of Animal Models of Serious Infections Caused by *Acinetobacter baumannii* and *Pseudomonas aeruginosa*

FDA Public Workshop
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Why are we here today?

- We recognize the potential clinical utility of antibacterial drugs that are active against a single species and the difficulties in developing such drugs
- While infections due to *P. aeruginosa or A. baumannii* are not infrequent, the frequency of occurrence of these bacteria at any one infection type is sufficiently low making it difficult to enroll a clinical trial
- In contrast to many other rare human diseases, certain acute bacterial infections pose unique challenges:
  - An urgent need to start effective therapy
  - Need for empiric therapy due to diagnostic uncertainty at the time of presentation
  - Difficult to identify patients who might develop such infections or maintain a registry of such patients

FDA Public Workshop

- Two-day workshop held on July 18 and 19, 2016
  - Day 1: Facilitating Antibacterial Drug Development for Patients with Unmet Need
  - Day 2: Developing Antibacterial Drugs that Target a Single Species
- Significant challenges of conducting a trial to show superiority in patients with multidrug-resistant organisms
- Importance of pharmacokinetics in target population
- Drugs active against an infrequently occurring single species
  - Practical difficulties in conducting a trial
  - Discussion about potential trial designs based on a hypothetical case; all of them have challenges and limitations
  - Potential roles for animal models of infection

http://www.fda.gov/Drugs/NewsEvents/ucm497650.htm

Options for Clinical Development (1)

- Noninferiority (NI) Trials:
  - A single NI trial at a body site (HABP/VABP; cUTI; cIAI) or in patients with HABP/VABP and/or bacteremia
  - Potentially feasible if greater uncertainty is acceptable (wider NI margins)
  - Will not need to limit enrollment to patients with *A. baumannii or P. aeruginosa* of a specific resistance phenotype
  - Availability of a rapid diagnostic test might help to identify patients, but will not change the frequency with which infections occur
  - Potential for confounding by concomitant therapies used to treat other pathogens in polymicrobial infections/empirically
  - The treatment effect of colistin-based comparator regimens may be difficult to assess

Options for Clinical Development (2)

- Superiority trials
  - Assess efficacy compared to best available therapy
  - Will enroll patients with *P. aeruginosa* or *A. baumannii* resistant to available therapy; may be difficult to identify/enroll enough patients in a clinical trial
  - Could enroll one or more body sites of infection
  - Determination of superiority over existing therapy can be difficult; opportunity to show superiority is time-limited and dependent on available therapy being suboptimal
  - Once new therapies become available, ability to demonstrate superiority becomes more difficult

Options for Clinical Development (3)

Conduct the study in patients with higher likelihood of having infections due to *P. aeruginosa* such as cystic fibrosis

- Depending on the study population, would need to identify the clinical condition to be treated (e.g., pulmonary exacerbations)
- Extrapolation to non-CF respiratory infections is challenging

Options for Clinical Development (4)

- Potential for approval under the Animal Rule:
  - Efficacy data is obtained from animal model(s) of infection; this might provide an option if an informative efficacy trial is not feasible
  - Animal efficacy data will be supplemented with clinical data from patients with a variety of infections caused by *P. aeruginosa* or *A. baumannii*

Developing a Product Under the Animal Rule

- **21 CFR 314.600-650:** Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible
- *Applies to certain new drug products that have been studied for their safety and efficacy in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances... definitive human efficacy studies cannot be conducted because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic …substance; and field trials…have not been feasible.*

Biologics 21 CFR 601.90-601.95

Animal Rule

Evidence of effectiveness from animal studies when:

1. There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;
2. The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;
3. The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and
4. The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans

21 CFR 314.610

Animal Rule (Additional Requirements)

- Postmarketing studies (e.g., field studies) to provide evaluation of safety and clinical benefit if circumstances arise in which a study would be feasible and ethical
- Restrictions to ensure safe use, if needed (e.g., restricting distribution to facilities or health care practitioners with special training, requiring specified types of follow up, or imposing record keeping requirements)
- Information in labeling to patients that explains that for ethical or feasibility reasons, the drug's approval was based on efficacy studies conducted in animals alone

21 CFR 314.610(b)(1) through (3) for drugs and 21 CFR 601.91(b)(1) through (3) for biological products

Examples of Animal Rule Drug Approvals

- Infectious Diseases:
  - Plague: Levofloxacin, ciprofloxacin and moxifloxacin
  - Inhalational Anthrax: Levofloxacin, raxibacumab, obiltoxaximab
- Non-Infectious Diseases:
  - Myelosuppression after radiological/nuclear incident: Pegfilgrastim and filgrastim
  - Cyanide poisoning: Hydroxocobalamin
  - Nerve gas: Pyridostigmine bromide

https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm391604.htm

Plague: Levofloxacin Example

- A placebo-controlled animal study in AGMs was conducted
- As levofloxacin is approved for other indications, including community acquired and nosocomial pneumonia, a study in one species was considered adequate
- AGMs were exposed to an inhaled mean dose of 65 LD50 of *Yersinia pestis* (CO92 strain)
- Animals were randomized to receive either a 10-day regimen of intravenous levofloxacin or placebo post-trigger
- Mortality in the levofloxacin arm was significantly lower (1/17) compared to the placebo group (7/7), $p<0.001$

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/020634Orig1s061,%20020635Orig1s067,%20021721Orig1s028TOC.cfm
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020634s066,020635s072,021721s033lbl.pdf

Today's Workshop

- We hope that discussions at today's meeting will help provide a better understanding of the relevant animal models of infection, the advantages and shortcomings of the currently available approaches, identify key areas for further work/development and the role that the animal models might play in the development of such drugs

Limited Population Pathway for Antibacterial and Antifungal Drugs

- 21st Century Cures Act signed into law on December 13, 2016; Sec. 3042 of 21st Century Cures Act
- The drug is intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs
- Labeling will include "Limited Population" in a prominent manner and the statement "This drug is indicated for use in a limited and specific population of patients"
- Pre-submission of promotional materials

Agenda for Today

- Clinical and Scientific Challenges
- Lessons Learned and Considerations for Animal Model Development
- Pathogenesis
- Approaches to Animal Model Development, Future Direction/Next Steps
- Panel Discussion (Audience Q and A)

Panel Members

- Tina Guina: NIH/NIAID
- David Boucher: BARDA
- Binh Diep: University of California San Francisco
- Daniel Zurawski: Walter Reed Army Institute of Research
- Matthew Lawrenz: University of Louisville
- David Andes: University of Wisconsin
- Joanna Goldberg: Emory University
- Robert Bonomo: Case Western University
- Samuel Miller: University of Wisconsin
- Jane Knisely: NIH/NIAID
- Edward Cox: FDA
- John Farley: FDA
- John Rex, MD: CARB-X, F2G Ltd.
- Andreas Wallnofer: Polyphor
- Robin Isaacs: Entasis Therapeutics
- Judith Hewitt: NIH/NIAID
- Gabriel Meister: Battelle Biomedical Research Center
- Julie Hutt: Lovelace Respiratory Research Institute
- Gianluigi Li Bassi: University of Barcelona*
- Helen Boucher: Tufts medical Center*

*via phone


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