

Regulatory Background

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Antimicrobial Drugs Advisory Committee

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Background

- Antibacterial drug development paradigms include standard and unmet need development programs
- In general, for standard development programs, noninferiority (NI) trials at specific body sites of infection are conducted; there is less uncertainty with regard to efficacy and safety
- Over the last few years there has been considerable focus on unmet need development programs
 - A draft guidance was issued in 2013
 - Clinical trials have been completed/ongoing using this approach

Background

- There is increasing interest in developing drugs that treat only a single bacterial species such as *Pseudomonas aeruginosa* or *Acinetobacter baumannii*
- Designing scientifically sound and feasible development programs for such drugs has been the focus of our most recent efforts and is the topic for discussion at today's meeting

Unmet Need Programs

- There is greater uncertainty and risk in such development programs; acceptable for life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists (21 CFR 312, subpart E)
- Clinical trial(s) must still meet the statutory standards for effectiveness as described in the FD&C Act
- Safety database of ~300 patients at the proposed dose and duration; will need additional data if safety concerns arise
- Thorough evaluation of in vitro activity and activity in relevant animal models of infection
- Risks and benefits will be communicated in labeling

21 CFR 312, Subpart E--Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses
Section 115 FDA Modernization Act

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products

Unmet Need: Trial Design Options

- Single NI trial in a body site of infection
- Single superiority trial in one body site of infection or pooled across body sites
- Single nested NI-superiority trial
- For an approved β -lactam being developed with a new β -lactamase inhibitor can rely in part on previous findings of safety and effectiveness of the β -lactam
- Superiority of adjunctive therapy plus Standard of Care (SOC) versus SOC

Single-species Specific Drugs

- We acknowledge the challenges with clinical trials for therapies that target a single species that occur infrequently
 - Sick patients and hence urgent need to start effective therapy
 - Need for empiric therapy due to diagnostic uncertainty at the time of presentation
 - Use of pre-study and concomitant effective therapy
 - Difficult to identify patients who might develop such infections or maintain a registry of such patients
- We recognize the potential clinical utility of such antibacterial drugs and have been working to find feasible solutions to develop such products

FDA Public Workshops

- July 18 and 19, 2016: Facilitating Antibacterial Drug Development for Patients with Unmet Need and Developing Antibacterial Drugs that Target a Single Species <http://www.fda.gov/Drugs/NewsEvents/ucm497650.htm>
- March 1, 2017: Current state and further development of animal models of serious infections caused by *A. baumannii* and *P. aeruginosa*:
<https://www.fda.gov/Drugs/NewsEvents/ucm534031.htm>

Unmet Need 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
- Day 1:
 - Trial design considerations for unmet need
 - Significant challenges of conducting a trial to show superiority in patients with multidrug-resistant organisms
 - Importance of pharmacokinetics in target population

Unmet Need Workshop: Day 2

- Discussion about the challenges in conducting trials for species-specific therapies
- Discussion about a hypothetical case of an antibacterial drug with activity limited to *P. aeruginosa*
- Potential trial designs were discussed; all of them have challenges and limitations
 - Noninferiority trials
 - Superiority trials
 - Studies in specific populations such as cystic fibrosis
 - Use of animal models of infection

Options Discussed

- Option 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 *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 prior effective therapy and concomitant therapies used to treat other pathogens in polymicrobial infections/empirically

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

Options Discussed

- Option 2: Superiority trials
 - Assess efficacy compared to best available therapy
 - Will enroll patients with *P. aeruginosa* 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
 - Demonstration of superiority over existing therapy can be difficult; opportunity to show superiority is usually time-limited and dependent on available therapy being suboptimal
 - Once new therapies become available, ability to demonstrate superiority becomes more difficult

Options Discussed

- Option 3: To study in patients with higher likelihood of having infections due to *P. aeruginosa* such as cystic fibrosis
- Option 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 available clinical data from patients with a variety of infections caused by *P. aeruginosa*

Animal Models Workshop

- Held on March 1, 2017, to discuss animal models of serious infections caused by *A. baumannii* and *P. aeruginosa*
- Participation from stakeholders including academia, industry, and other government agencies
- Programs for two products that are currently in development were discussed
- Key topics discussed
 - Use of the Animal Rule to support the approval of products for plague and anthrax
 - Role of animal models, key attributes and shortcomings of some of the currently used animal models
 - Given the urgent need for such therapies, the role of animal models to support the limited clinical data that might be feasible to obtain

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Broad Agency Announcement

Solicitation Number: FDABAA-17-00123N
Agency: Department of Health and Human Services
Office: Food and Drug Administration
Location: Office of Acquisitions and Grants Services - Rockville

Notice Details Packages

Print Link

Original Synopsis
Feb 23, 2017
1:50 pm

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Solicitation Number: FDABAA-17-00123N
Notice Type: Combined Synopsis/Solicitation

Synopsis:
Added: Feb 23, 2017 1:50 pm
Food and Drug Administration (FDA) solicitation for research and development to support regulatory science and innovation. FDA anticipates that research and development activities awarded under this Broad Agency Announcement (BAA) will serve to advance scientific knowledge to accomplish its mission to protect and promote the health of our nation.

This announcement will remain open until further notice.

ALL FILES

- [FDABAA-17-00123](#) Feb 23, 2017
- [FDABAA-17-00123.pdf](#)

GENERAL INFORMATION

Notice Type: Combined Synopsis/Solicitation
Posted Date: February 23, 2017
Response Date: -
Archiving Policy: Manual Archive

[FDABAA-17-00123N](#): Research proposals focused on advancing the development of animal models of serious infections caused by Acinetobacter or Pseudomonas; proposals received for FY17 funding are under review.

Development Programs for Single-Species Drugs

- What is achievable with such programs?
 - Limited clinical data package
 - Evidence of activity and efficacy in relevant animal models of infection
 - Robust pharmacokinetic/pharmacodynamic (PK/PD) data package
 - Limited human safety information and nonclinical safety data

Clinical Data Package (NI Trials)

- Although difficult to conduct, might be a feasible option; however, there may be greater uncertainty in the treatment effect with such programs
- The use of prior and concomitant effective therapies in a reasonable fraction of the patient population can confound the assessment of the effect of an investigational drug
- A single NI trial using a wider NI margin than would typically be used for a standard development program
- For HABP/VABP, we allow for an NI margin of 10% for standard development programs and 12.5% for therapies that address an unmet need
- For a single species specific drug, we are willing to consider an NI margin equal to the estimated treatment effect

Clinical Data Package (Superiority Trials)

- Clear finding of efficacy
- Feasible to conduct for the first one or two drugs that are being developed as it might be possible to demonstrate superiority over current SOC
- As SOC changes when new therapies become available, the trial may become infeasible and/or unethical at the point a new SOC replaces the less than adequate comparator treatment
- Given these challenges, Sponsors are generally not willing to design the trial to demonstrate superiority

Animal Models

- As activity and efficacy in relevant animal models of infection will play a critical role in these development programs, it is important that:
 - The effect is demonstrated in more than one animal species expected to react with a response predictive for humans
 - The animal model(s) of infections are relevant to the clinical condition being studied in humans
 - The study endpoint in the animal models is similar to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity



What might be potential outcomes of these programs?

Potential Scenarios

1. The best scenario is one where a successful clinical trial, either superiority/NI is completed and there are no major safety signals of concern
2. A second possibility is that the clinical trial results strongly suggest lack of a beneficial effect
3. A third possibility is that the efficacy of the drug could not be discerned in the clinical trial due to multiple confounders
 - Evidence of efficacy might come from animal models of infection
4. Although efficacy is demonstrated, safety concerns do not allow for a favorable risk-benefit assessment

Safety

- Safety of the product will be assessed in nonclinical studies and based on the signal, if any, appropriate monitoring may be included in the clinical trials
- The database at the proposed dose and duration may be very limited ~300 patients; additional data if there is a safety signal
- For such products there might be a need for additional safety data, e.g., through postmarketing requirements or enhanced pharmacovigilance
- It is important that such products be used judiciously and safety be closely monitored

21st Century Cures Act

- Signed into law on December 13, 2016
- Title III, Subtitle E – Antimicrobial Innovation and Stewardship
- Sections that primarily impact anti-infective products:
 - Section 3042: Limited population pathway (LPAD)
 - Section 3044: Susceptibility test interpretive criteria for microorganisms; anti-microbial susceptibility testing devices

Limited Population Pathway for Antibacterial and Antifungal Drugs

- 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

Today's Meeting

- The two key topics we would like to discuss at today's meeting are:
 - The development programs for single-species specific antibacterial drugs where the bacterial species is not commonly identified in any one infection
 - Should a clinical development program not be feasible or the clinical data not be interpretable, what the role of the animal models of infection would be

Question 1

- Discuss the unmet medical need for single species specific products and the risks and benefits of the development proposals presented; please provide any additional recommendations you might have for developing such products.

Question 2

- While every effort will be made to perform human clinical trials, performing clinical trials for antibacterial drugs that treat a single species of bacteria when the target species infrequently causes infections will be challenging and data collected may not be interpretable or may be very limited. Should this circumstance arise, it may be useful to consider whether animal models of serious bacterial infections can provide useful information to assess the activity and efficacy of the drug. In such a situation, please discuss the following:
 - The types of animal models and appropriate endpoints that you think might be useful to assess the efficacy of an investigational agent.
 - If there is a situation where efficacy is principally demonstrated in animal models of infection and only limited clinical trial data are available in humans, how might such a product be used clinically?

Outline for the Day

- Summary of the March 1 workshop:
 - Yuliya Yasinskaya MD
- Case presentations:
 - An example of a drug with activity against *A. baumannii* only:
Robin Isaacs MD
 - An example of a drug with activity against *P. aeruginosa* only:
Peter Kim MD MS
- Infectious Diseases Society of America (IDSA) Presentation
 - Trish Perl-DeLisle MD
- Clarifying Questions
- Open Public Hearing
- Committee Discussion



March 2017 FDA Public Workshop Summary

Antimicrobial Drugs Advisory Committee Meeting
April 13, 2017

Yuliya Yasinskaya, MD
Division of Anti-Infective Products
FDA

March 1, 2017 FDA Public Workshop



Morning Session

- Clinical and Scientific Challenges
 - Clinical perspective
 - Challenges in clinical trial design
 - Lessons learned from animal models for biothreat agents
- Pathogenesis of *Pseudomonas* and *Acinetobacter* infections

Afternoon Session

- Pharmacokinetic/Pharmacodynamic (PK/PD) considerations
- Animal models current status and future directions

Panel Discussions



Clinical and Scientific Challenges

Clinical Challenges

- Critical unmet need clinical scenarios
- Challenges in clinical trial design
 - Narrow spectrum of activity/need for concomitant therapies
 - Infrequent infections spanning different organs
 - Pre-study antibacterial drug use
 - Microbiologic confirmation not available at baseline hence necessitating empiric treatments
 - Superiority design is problematic requiring randomization to likely ineffective therapy and becomes unfeasible with availability of new treatments
- PK/PD targets should be established prior to clinical trials

Role of Animal Models in Drug Development



- Model of activity vs. model of disease
- Small animal models
 - screen for candidate product activity
 - establish and characterize PK/PD target
- Combination of animal models susceptible to clinically relevant bacterial strains with positive and negative antibacterial controls to supplement limited clinical trial data
- Animal models for efficacy trials to support approval under the Animal Rule



Examples of Clinical Development Programs Targeting Single Pathogens

- Entasis Therapeutics ETX2514SUL, a novel non- β -lactam, β -lactamase inhibitor in combination with sulbactam to target *A. baumannii*
- Polyphor Ltd. program for murepavidin targeting outer membrane of *P. aeruginosa* including multi-drug resistant strains
 - presented today by Dr. Peter Kim, FDA

Animal Models for CT Indications



- African Green monkey (AGM) for pneumonic plague
- Cynomolgus macaque for pneumonic tularemia
- New Zealand White rabbit model for inhalational anthrax
 - Characterization of disease pathogenesis and histopathology in humans and animals
 - Describe clinical course of the disease (observation/telemetry)
 - Delineate appropriate challenge dose with clinically relevant isolate, specific (Protective Antigen toxemia, bacteremia) and non-specific indicators (signs and symptoms) of established disease
 - Identify clinically acceptable trigger and timing for intervention
 - Lengthy iterative process to final therapeutic model
 - Quality management system and close interaction with FDA are critical

Pathogenesis of *P. aeruginosa* and *A. baumannii* in humans and animals

PK/PD considerations

Pathogen Specific Determinants



- *P. aeruginosa*
 - Opportunistic pathogen
 - Highly adaptable
 - Distinct virulence factors depending on site and source of the infection
 - Acute versus chronic infections
- *A. baumannii*
 - Not opportunistic in man, but in animals
 - In vitro assays don't predict virulence in vivo
 - Non-mammalian hosts for characterization of novel virulence factors and resistance mechanisms

PK/PD Assessment in Animal Models

- Understanding PK/PD for various models of infection
- Murine models of infection assessing bacterial burden
 - PD parameters for sepsis, skin and lung infections
 - Testing different clinical isolates with variable MICs
 - Good correlation to clinical outcomes
 - Limitations of lung infection model
 - Differences in lung anatomy/physiology
 - Pattern recognition receptors
 - Antimicrobial secretions
 - Lack of neutrophils, defensins
 - Alveolar macrophage and pulmonary epithelial lining fluid penetration differences

Currently Available Animal Models

Neutropenic Murine Model of *P. aeruginosa* Pneumonia



- Clinically relevant strains and inocula with various susceptibility profiles
- Clinical signs observed, i.e. hypothermia, bradycardia, hypoxemia and disorientation, predictive of imminent mortality
- Target organ bacterial burden and/or dissemination rates to assess disease progression/dissemination
- Drugs and biologics alone and in combination could be tested

A. baumannii Infections in the Murine and Pig Models



- Pulmonary Murine (neutropenic) model
 - Multiple strains tested
 - Clinical relevant virulent AB5075 strain infection also disseminates
 - Outcome: survival and organ bacterial burden
 - Clear dose response with rifampin (positive control) in bacterial burden reduction and survival
- Wound Porcine and Murine (neutropenic) models
 - Punch biopsy
 - Use of positive controls
 - Wound area measuring, time to closure
 - Colony forming units/g tissue
 - Gross and histopathology
 - Biofilm/cytokine/chemokine evaluation

Rabbit Model of *P. aeruginosa* Pneumonia



- Closely resembles human disease
 - Inoculum
 - Pathogenesis
 - Symptomatology
- Continuous ventilation
- Allows for vital signs, lab, electrocardiogram, blood gas, blood culture monitoring
- Mortality due to shock or multi-organ failure

Ventilated Pig Model of *P. aeruginosa* Pneumonia



- Similar to humans:
 - Anatomy and physiology
 - Ventilator-associated pneumonia (VAP) disease pathogenesis replicated (oral secretion aspiration and gravity dissemination)
 - Lack of significant hemodynamic instability
 - Lung pathology (right middle and lower lobes, left lower lobe, but not right upper lobe)
- Intensive care-like settings (sedated paralyzed, ventilated)

Panel Discussion

Key Discussion Points

- Models similar to AGM for plague will be difficult to develop for *P. aeruginosa* and *A. baumannii* due to variable
 - Intrinsic degree of virulence
 - Susceptibility of the animal hosts
- Consistent results across various animal models with clinically relevant strains will be important
 - Mammal vs non-mammal
 - Neutropenic vs immune competent
 - Small vs large
- Sensitivity of animal model assessed by using positive and negative antibacterial controls
- Disease biomarkers monitoring and histopathological assessments
- Testing diverse clinically relevant isolates with a well described pedigree in animal models

Summary

While no single animal model might be best suited to study infections caused by *P. aeruginosa* and *A. baumannii*, there is utility to each of the models and with some short-term refinements and continued developmental work, animal models can provide useful information to support the development of therapeutic agents



Example of a Development Program Targeting *P. aeruginosa*

Peter Kim MD MS
Medical Officer
Division of Anti-Infective Products

Antimicrobial Drugs Advisory Committee Meeting
April 13th 2017



Example of a Development Program

Targeting *P. aeruginosa*: POL7080

- POL7080 is an antibacterial drug with activity limited to *P. aeruginosa* (no activity vs. Gram-positives or other Gram-negatives, including Enterobacteriaceae)
- Targets an outer membrane protein of *P. aeruginosa*
- While the Sponsor has elected not to present at today's meeting, FDA will present a summary of the development program based on information discussed at the FDA Public Workshop on March 1, 2017;
<https://www.fda.gov/Drugs/NewsEvents/ucm534031.htm>
- FDA's presentation of this information should not be considered an endorsement of the development program for POL7080

Background

- In a neutropenic mouse lung infection model, increasing total daily doses of POL7080 resulted in greater \log_{10} colony forming units/gram reductions of *P. aeruginosa*, including isolates resistant to polymyxin B
- Sponsor has used pharmacokinetic/pharmacodynamic (PK/PD) modeling in an effort to determine the PD target and inform selection of a dose for clinical testing

Clinical Studies

- Sponsor has completed six Phase 1 studies and two Phase 2 studies
- Phase 1:
 - Included drug-drug interaction studies with colistin and amikacin, as well as, assessment of PK and safety in participants with renal impairment
- Phase 2:
 - Non-Cystic Fibrosis Bronchiectasis
 - Ventilator-Associated Bacterial Pneumonia (VABP) in 12 patients with confirmed *P. aeruginosa*

Phase 3 HABP/VABP Trial (1)

- Sponsor presented a proposal for a multicenter, randomized, parallel group noninferiority (NI) trial to evaluate the efficacy, safety, and PK of POL7080 in patients with hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) due to suspected *P. aeruginosa*
- Patients would be randomized 1:1 to the following treatment groups for single coverage against *P. aeruginosa*
- Study arm: POL7080 + ertapenem
Control arm: meropenem
- Ertapenem 1 gram intravenous daily was modeled and appears to achieve acceptable levels of exposure in VABP patients
 - In U.S., ertapenem is approved for community-acquired pneumonia and not HABP/VABP; ertapenem does not have activity against *P. aeruginosa*

Phase 3 HABP/VABP Trial (2)

- Protocol would allow for concomitant use of amikacin for empiric dual anti-pseudomonal coverage in both arms at the discretion of investigators until culture and susceptibility results are available, for a maximum total duration of 72 hours
- Investigators would decide whether to administer dual coverage prior to randomization
- Primary endpoint: 28-day all-cause mortality in the microbiologic intent-to-treat population (confirmed *P. aeruginosa*)
- A rapid diagnostic test would be used to aid in identifying patients with suspected *P. aeruginosa*
- Based on feedback from key opinion leaders, the Sponsor considers the proposed trial design feasible at centers with <10% multi-drug resistant *P. aeruginosa*

Phase 3 trial challenges

- At 22% incidence of *P. aeruginosa*, the Sponsor estimated that 3,064 patients would need to be randomized if a 10% NI margin was specified
- Superiority difficult to demonstrate
- Challenge enrolling patients in a study treating *Pseudomonas* with monotherapy
- Difficult to discern treatment effect of POL7080 in the context of concomitant antibacterial drugs used to treat other pathogens that may also cover *Pseudomonas*
- Challenges with obtaining consent in HABP/VABP patients

