# Case Study: FDA Perspective

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# Narrow Spectrum Drugs: General Considerations

- We recognize the potential clinical utility for antibacterial drugs that are active against a single species

- We also recognize that such drugs are difficult to study when the single species that the drug is active against occurs rarely

- Although *P. aeruginosa* is not a rare cause of certain infections, the frequency of occurence at any one body site is sufficiently low to make enrolling in a clinical trial difficult

- Some infections such as HABP/VABP where *P. aeruginosa* is more frequently identified, tend to be polymicrobial; need for concomitant therapy with overlapping spectrum of activity

- Rapid diagnostics could help some, but will not solve all these problems

# Narrow Spectrum Drugs: Challenges

- In contrast to other rare human diseases, acute bacterial infections pose unique challenges:
    - An urgent need to start therapy as time to initiating effective therapy impact outcomes
    - Diagnostic uncertainty at the time of presentation, necessitating empiric therapy in many instances
    - Difficult to identify patients who might develop such infections or maintain a registry of such patients except in very limited circumstances
    - Patients present at local healthcare facilities rather than at a special facility

# Characteristics of X-1

- Appears to address an unmet need; novel mechanism of action
- In vitro studies do not suggest a high likelihood of resistance development
- Safety profile from nonclinical studies seems reasonable; identified toxicities appear to be monitorable; safety margin at the proposed dose
- Activity demonstrated in animal models of infection
- Proof of concept study showed evidence of microbiologic activity
- Dosing rationale appears adequate
- Dosing for patients with renal impairment known; will allow for enrollment of patients with renal dysfunction

# Options for Phase 3 development program

- **Option 1:** Noninferiority Trials:
  - A single noninferiority trial at a body site (HABP/VABP; cUTI; cIAI)
  - A single noninferiority trial in patients with HABP/VABP and/or bacteremia
- **Option 2:** Superiority trials:
  - A single trial pooling across body sites (cIAI, HABP/VABP, cUTI)
  - A single trial at a body site
- **Option 3:** Trial(s) in populations at higher risk of infections due to *P. aeruginosa*
  - Patients with cystic fibrosis/non-CF-bronchiectasis
- **Option 4:** Establish efficacy under the Animal Rule

# Option 1 (a): NI trial at single body site (HABP/VABP)

- **Pros:**
  - Potentially feasible if greater uncertainty is acceptable (wider NI margins)
  - No need to limit enrollment to only patients with *P. aeruginosa* of a specific phenotype
- **Cons:**
  - Difficult to enroll adequate number of patients with *P. aeruginosa* in a standard NI trial
  - Availability of a rapid diagnostic test might help with identifying patients with *P. aeruginosa,* but will not change the frequency with which *P. aeruginosa* causes infections

# NI trial at single body site (HABP/VABP, contd.)

- **Cons (contd.)**
- Need for concomitant antibacterial drugs to treat other potential Gram-negative organisms
  - One consideration is to use ertapenem; however not indicated for HABP/VABP; need to assess if it will be considered clinically acceptable
- Double coverage for *P. aeruginosa*
  - Typically for treatment of HABP/VABP due to *P. aeruginosa,* dual therapy used (monotherapy acceptable in certain situations); confounds assessment of treatment effect of X-1
  - Clinicians may be hesitant to de-escalate empiric therapy even after *P. aeruginosa* is identified as the etiologic agent

Management of Adults With HAP/VAP: 2016 Clinical Practice Guidelines by IDSA and ATS

# NI trial at single body site (cont'd)

- Sample size for a HABP/VABP trial using all-cause mortality as primary endpoint and the following assumptions:
  - 20% mortality rate
  - Two -sided $\alpha=0.05$
  - 80% power, 1:1 randomization
  - NI Margin:10-20%
  - Prevalence of *P. aeruginosa:* 10%-20%

# Sample Sizes for an NI HABP/VABP Trial

| | Noninferiority Margin | | | |
|---|---|---|---|---|
| | 10% | 12.5% | 15% | 20% |
| Prevalence of PA | **Total Number of Patients (Patients with PA only)** | | | |
| 10% | 5040 (502) | 3220 (322) | 2240 (224) | 1260 (126) |
| 15% | 3360 (502) | 2146 (322) | 1493 (224) | 840 (126) |
| 20% | 2520 (502) | 1610 (322) | 1120 (224) | 630 (126) |

An acceptable margin of effectiveness of an active control drug relative to placebo for HABP/VABP is 20%

# Option 1 (a): NI trial at single body site

- complicated UTI (cUTI)
  - Although *P. aeruginosa* may cause mono-microbial infections at this body site, incidence is still low and such a trial might not be feasible
  - Efficacy results from cUTI trials may not translate to other body sites given that drugs may concentrate in the urine during excretion resulting in higher exposures compared with other body sites, e.g., lung
- Burns and surgical site infections
  - Difficult to study, not very common, trial design and endpoints need further discussion

# Option 1 (b): NI trial pooling across body sites

A single noninferiority trial in patients with HABP/VABP and/or bacteremia; all-cause mortality as endpoint

- **Pros:**
  - Might make the trial more feasible than a trial in HABP/VABP alone
- **Cons:**
  - Maybe difficult to discern if the test drug has a deficit in efficacy at one or more body site
  - Size of the treatment effect varies across different infections

# Option 2: Superiority trial

- Assess the superiority of Drug X-1 vs. best available therapy
    - Enroll patients with *P. aeruginosa* resistant to available therapy
    - Could enroll one or more body sites of infection
- **Pros:**
    - Provides direct evidence of treatment effect
- **Cons:**
    - Determination of superiority over existing therapy can be difficult
    - Pooling across different body sites can impact on our ability to see a potential deficit in one or more body sites
    - May be difficult to identify/enroll enough patients in a clinical trial

# Prevalence of *P. aeruginosa*

- In a surveillance study in patients with PHP/VABP, 1730/8201 (21%) of the organisms were *P. aeruginosa*

- The incidence of meropenem nonsusceptibility in *P. aeruginosa* was 22% (382/1730)

- Among the meropenem-nonsusceptible *P. aeruginosa,* the incidence of amikacin resistance was approximately 13%

- The incidence of both meropenem and amikacin resistance in the overall population was approximately 0.8%

- In an all-comer population, to find one patient with *P. aeruginosa* resistant to both meropenem and amikacin, one would need to enroll about 122 patients

PHP: Pneumonia in hospitalized patients
Flamm et al. Int J Antimicrob Agents. 2016 Mar;47(3):235-42

Incidence of *P. aeruginosa* nonsusceptible to meropenem (MIC ≥4mg/L) and amikacin resistance

|  | EX-US | US |
|---|---|---|
| **Non-VAP** | 28/218 (12.8%) | 8/157 (5.1%) |
| **VAP** | 29/112 (25.9%) | 2/33 (6.1%) |

Incidence of *P. aeruginosa* nonsusceptible to meropenem (MIC ≥4mg/L) and amikacin resistance

|  | EX-US | US |
|---|---|---|
| **Non-VAP** | 28/3281 (0.9%) | 8/3213 (0.2%) |
| **VAP** | 29/1015 (3.0%) | 2/692 (0.2%) |

# Superiority Trials

Sample size for a HABP/VABP trial using all-cause mortality as primary endpoint and the following assumptions:

- 1:1 randomization
- Two-sided α = 0.05
- 80% power
- Control group mortality rate: 40%
- Mortality rate in test arm: 20-30%
- Frequency of MDR *P. aeruginosa:* 5%-25%

# Sample Size

| Frequency of MDR PA | Mortality Rate in Test Arm | Number of Subjects with MDR PA | Total Number of Subjects |
|---|---|---|---|
| 5% | 30% | 708 | 14160 |
| 5% | 25% | 300 | 6000 |
| 5% | 20% | 158 | 3160 |
| | | | |
| 10% | 30% | 708 | 7080 |
| 10% | 25% | 300 | 3000 |
| 10% | 20% | 158 | 1580 |
| | | | |
| 15% | 30% | 708 | 4720 |
| 15% | 25% | 300 | 2000 |
| 15% | 20% | 158 | 1053 |
| | | | |
| 25% | 30% | 708 | 2832 |
| 25% | 25% | 300 | 1200 |
| 25% | 20% | 158 | 632 |

# Option 3: Patient population likely to have *P. aeruginosa* infections

Examples might include patients with cystic fibrosis or bronchiectasis

- **Pros:**
  - Higher likelihood of infections due to *P. aeruginosa*
- **Cons:**
  - Depending on the study population, we would need to identify the clinical condition to be treated (e.g., pulmonary exacerbations)
  - This option may have similar issues as with Option #1 (treating HABP/VABP) regarding concomitant therapy
  - Extrapolation to non-CF respiratory infections is challenging

# Option 4: Use 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 <u>serious or life-threatening conditions</u> caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances... <u>definitive human efficacy studies cannot be conducted</u> because it would be <u>unethical</u> to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic ...substance; and field trials...have <u>not been feasible</u>.*

Biologics 21 CFR 601.90-601.95

# Evidence of effectiveness from animal studies

1. There is a reasonably well-understood <u>pathophysiological mechanism</u> of the toxicity of the substance and its prevention or substantial reduction by the product;

2. The effect is demonstrated in <u>more than one animal species expected to react with a response predictive for humans</u>, 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 <u>animal study endpoint </u>is clearly related to the desired benefit in humans, generally the <u>enhancement of survival or prevention of major morbidity</u>; 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 <u>selection of an effective dose in humans</u>.

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

# Option 4: Use Animal Rule (contd.)

Obtain efficacy data from adequately characterized animal model(s)

- Could be supplemented with clinical data from patients with a variety of infections caused by *P. aeruginosa* in one or more descriptive studies

- **Pros:**
  - If an informative efficacy trial is considered not feasible, might provide an option to assess efficacy

- **Cons:**
  - There are currently no adequately characterized animal models for the indications being considered
  - Unlike with biothreat agents, it is ethical to conduct human efficacy trials; however, feasibility of conducting such trials is the issue

# Option 4: Use Animal Rule (cont'd)

- **Cons (cont'd):**
  - Unlike drugs developed for biothreat indications, if approved, such a product would likely be used in a broad population and potentially used on an empiric basis
  - What would the field trial look like?
    - Required when feasible and ethical
    - If able to conduct right after approval, then invalidates need for approval under the Animal Rule
    - Post-approval study will likely face same challenges that were encountered pre-approval
  - May set a precedent for other clinical conditions of low prevalence

# Animal Rule Drug Approvals

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

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/020634s061,020635s067,021721s028ltr.pdf
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/019537Orig1s083,019847Orig1s055,019857Orig1s063,020780Orig1s041ltr.pdf
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/021085Origs060,021277Orig1s056ltr.pdf
http://www.cdc.gov/plague/maps/index.htm
http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm391604.html

# Animal Rule: Plague Example

- African Green Monkey (AGM) model of primary pneumonic plague was developed to provide a platform for testing therapeutic interventions
- Model using mortality outcome in symptomatic disease was evaluated in different laboratories
  - Disease progression described
  - Potential triggers for therapeutic intervention were evaluated
- Limited human data was available; variability in timing of clinical presentation, interventions and outcomes

# Natural History Studies (AGMs)

- Experimentally naïve healthy adult male and female AGMs

- Aerosol exposure target: 100 x LD$_{50}$ with *Y. pestis* CO92 strain

- Clinical and laboratory monitoring performed

- Gross and microscopic pathology assessed in AGMs who succumbed to disease

# AGM Studies: Key Characteristics

- Exposures ranged from 9-1150 x LD50
- Clinical Features: Fever, loss of appetite, respiratory distress, lethargy, respiratory secretions
- Laboratory Tests:
  - Neutrophilic leukocytosis, LFT, coagulation abnormalities
  - Onset of bacteremia: 30-94 hours
  - Radiologic infiltrates
- Pathology: Fibrinosuppurative, hemorrhagic pneumonia

# AGM Model and Human Primary Pneumonic Plague

| DATA ELEMENT | AGM | Human |
|---|---|---|
| **Characteristics of the Agent** | | |
| Challenge agent | *Y. pestis* CO92 strain | *Y. pestis* (CO92 strain was isolated from a human with pneumonic plague) |
| Pathogenic determinants | F1 capsular antigen, LcrV and Yersinia outer membrane proteins (yops), plasminogen activator (Pla) | |
| Route of exposure | Aerosol (head only exposure) | Direct aerosol exposure to a close contact with pneumonic plague or bioweaponized aerosol |
| Quantification of exposure | 20 to >1000 x LD 50 | Infectious inoculum 100-500 organisms. Variable during close aerosol contact, high exposure possible if bioweaponized |

# AGM Model and Human Primary Pneumonic Plague

|  | **AGM** | **Human** |
|---|---|---|
| **Pathophysiologic Comparability** | | |
| Time to onset of disease/condition | 26-80 hours (1-3) days to fever onset | 1-6 days to fever and other symptom onset |
| Time course of progression of disease/condition | Time to death 55-139 hours (2-6 days, median 3 days) | With no antibiotics survival 2-6 days (median 3 days) |
| Signs and Symptoms | Fever, hunched posture, lethargy, tachypnea, tachycardia, cough, bloody respiratory secretions<br><br>Neutrophilic leukocytosis, coagulation abnormalities | Abrupt onset of fever, chills, lethargy, headache, cough, hemoptysis, ARDS, DIC, multiorgan failure, shock<br><br>Neutrophilic leukocytosis, thrombocytopenia, acidosis |
| Radiology | Infiltrates | Multilobar consolidation, cavities, bronchopneumonia |
| Pathology | Hemorrhagic pneumonia | Hemorrhagic pneumonia |

# AGM Model and Human Primary Pneumonic Plague

|  | AGM | Human |
|---|---|---|
| **Host Susceptibility and Response to Etiologic Agent** | | |
|  | Highly susceptible; if symptomatic disease is uniformly fatal | Highly susceptible, uniformly fatal if untreated |
| **Trigger for Intervention** | | |
|  | 4 hours after onset of fever (>1.5° C over baseline for 2 hours) | Variable; depends on high index of suspicion, hemorrhagic pneumonia; positive smear or culture, titers of anti-F1 ab |

# Design Considerations for Animal Efficacy Studies

| Characteristics | |
|---|---|
| Endpoint | Mortality |
| Timing of intervention | After fever onset |
| Route of administration of test drug | Intravenous |
| Dosing regimen | Humanized |

# 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

# Summary

- Characteristics of Drug X-1 appear to address an unmet medical need

- Under the current paradigm, studying drugs such as X-1 that are active only against a single species that occurs infrequently can be very challenging

- Discussed some potential development options, all of them have limitations

- Even if one were to consider the Animal Rule, more work needs to be done to develop specific animal models of infection for assessment of efficacy for the clinical conditions being considered