FDA Briefing Document

Developing Antibacterial Therapies Targeting a Single Bacterial Species

Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)

April 13, 2017

The committee will discuss developmental pathways for antibacterial drugs targeting single bacterial species that infrequently cause infections

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought up for discussion the issues and potential regulatory approaches for the development of antibacterial products targeting a single bacterial species to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Introduction

The purpose of this meeting is to discuss the challenges associated with developing antibacterial drugs that target a single bacterial species that infrequently causes infections (e.g. *Pseudomonas aeruginosa* or *Acinetobacter baumannii*). In general, antibacterial drugs that are developed target either gram-positive or gram-negative bacteria, or in some instances target both groups of bacteria. Currently, there is interest in developing antibacterial drugs and monoclonal antibodies with activity against a single bacterial species.

In this briefing document, we have summarized some recent public discussions we have had on this topic, including two examples of antibacterial drugs that target a single organism (one each for *P. aeruginosa* or *A. baumannii*), and discuss some options for clinical development of such products. Sponsors developing drugs that target a single bacterial species voluntarily participated in the public discussions. The information included in the two examples is based on presentations made by the respective Sponsors at the March 1, 2017 public workshop.

We would like the committee to discuss the challenges with developing such products, discuss the clinical utility and likely use of such products, and provide advice regarding other potential development options that we should consider. The purpose of the meeting is not to specifically discuss the two examples we have provided, but to use them as a framework for the discussion.

If the therapy targeting a single bacterial species treats a bacterium that is identified relatively frequently at a given body site of infection such as *Staphylococcus aureus* in acute bacterial skin and skin structure infections, then trials are readily feasible. If the target pathogens occur infrequently at any body site of infection (e.g., *P. aeruginosa* or *A. baumannii*) and the effect size is about the same as for other antibacterial drugs (e.g., a 20 % improvement in outcomes), a clinical development program can be challenging. This is essentially a problem of studying a low frequency event for which therapy must be initiated urgently/emergently and the first doses of treatment are very important in determining outcomes. There are important differences in serious acute bacterial infections that limit the applicability of the approaches used for many of the rare human diseases (often metabolic disorders). In acute bacterial infectious diseases:

- there is an emergent, urgent need to start therapy and early doses are critically important in impacting outcomes.
- there is often diagnostic uncertainty for a serious acute infectious disease whereas, for rare metabolic disorders, the diagnosis is generally well-established in advance of trial enrollment.
- clinical outcomes for these infections are achieved within days to a week or two.

- patients present to the nearest healthcare institution rather than a referral center and, unlike rare metabolic disorders, there is no registry of who might be eligible for a trial based on an infection / the condition.

The possible indications we have considered for antibacterial drugs with activity against only *P. aeruginosa* or *A. baumannii* include Hospital-Acquired Bacterial Pneumonia/Ventilator-Associated Bacterial Pneumonia (HABP/VABP), complicated urinary tract infections (cUTI) and bloodstream infections.

The prevalence of these pathogens in recently conducted HABP/VABP trials is ~10 % and in cUTI trials is ~2 %. In recent publications, *P. aeruginosa* has been isolated in 10%-20% of VABP, 7-10% of urinary tract infections and 4.3% of bloodstream infections, and *A. baumannii* has been isolated in 5%-10% of cases of VABP, 1%-2% of urinary tract infections , and 1.3% of bloodstream infections [1, 2, 3, 4].

Summary of the FDA Public Workshop held on July 18th and 19th, 2016 (https://www.fda.gov/Drugs/NewsEvents/ucm534031.htm)

A two-day public workshop was held on July 18th and 19th to discuss developing antibacterial drugs for patients with unmet need. On Day 1, the meeting focused on general considerations in developing antibacterial drugs for patients with an unmet medical need and on Day 2, the discussion pertained to developing antibacterial drugs that target a single species and the species occurs infrequently in any particular infection.

The meeting was well attended with engagement and thoughtful discussion from the presenters, panelists, and participants. The meeting fostered an increased understanding of difficulties in developing such drugs and potential options for performing clinical trials in this space to evaluate antibacterial drugs.

[1] Management of Adults With HAP/VAP: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016 Sep 1; 63(5).
[2] Weiner LM, et al. Antimicrobial-Resistant Pathogens Associated With Healthcare-Associated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. Infect Control Hosp Epidemiol. 2016 Nov; 37(11):1288-1301.
[3] Principles and Practice of Infectious Diseases, 8th edition. Chapters 221 and 224.
[4] Wisplinghoff H et al. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis. 2004 Aug 1;39 (3):309-17.

Day 1: Challenges in Development Programs for Antibacterial Drugs Addressing an Unmet Need

Discussion on the first day focused on general aspects of development programs for antibacterial drugs being developed to address an unmet need. Key discussion points included:

- Difficulties in conducting superiority trials: It was recognized that occasionally, clinical trials will be able to demonstrate superiority. However, Sponsors noted that planning to demonstrate superiority is generally not realistic and may be too risky for them. Additionally, the ability to demonstrate superiority is often time-limited because it is dependent on "inadequate" therapy, and as new therapeutic options become available, the opportunities to show superiority will be diminished. Once a new antibacterial agent is approved that changes the standard of care (SOC), it would need to be incorporated into the trial to meet SOC and this may take away the opportunity to show superiority. Achaogen, the developer of plazomicin, presented the difficulties they encountered in conducting a superiority trial in patients with carbapenem-resistant Enterobacteriaceae (CARE). They had planned to enroll ~ 300 patients and due to enrollment challenges, the study was stopped after less than 100 patients were enrolled. The main reasons cited for prescreen failure were that the organism was not a CRE and that patients had received more than 72 hours of empiric antibacterial therapy.
- Noninferiority (NI) Trials: In general, there was agreement that NI trials are the best option available. There was discussion about the use of wider NI margins than that used in traditional development programs and that given the unmet need there was willingness to accept greater uncertainty.
- Pharmacokinetics and Dose Selection: The importance of pharmacokinetics and dose selection in sicker patients/patients with comorbidities and the differing pharmacokinetics based on the type of infection (e.g., cUTI vs. cIAI vs. HABP/VABP vs. CABP) was discussed. The importance of assessing PK in patients with the infection type for which the drug is being developed was also discussed. Achaogen also presented data to show that there was a broader range of baseline renal function in their CARE study and more variable drug exposure compared to the cUTI trial in an "all-comer" population. There was recognition that it is important to select the appropriate dose and duration of therapy depending on site of infection. In the last decade, as trial designs have improved, we have seen several drugs with efficacy deficits in different body sites.
- Statistical Considerations: The potential use of Bayesian methodologies to borrow information from across body sites of infection was discussed.

Day 2: Development Programs for Antibacterial Drugs Targeting Single Bacterial Species

Discussion on the second day focused on potential development programs for antibacterial drugs that target a single species of bacteria that occur infrequently in any particular infection type.

For the workshop, a hypothetical case was developed of a drug that has activity only against *P. aeruginosa* and several different development options were presented. There was a robust discussion by the panel members and the audience regarding the pros and cons of the various options.

Case Study:

The example presented to the group illustrated challenges in accruing patients for a clinical trial to generate evidence to assess the efficacy of the drug. The following is an abbreviated version of the hypothetical case that was discussed:

Drug X-1 is an injectable antibacterial drug with activity limited to *P. aeruginosa*. It acts via a new mechanism of action on a novel target that is unique to *P. aeruginosa*. Signals for hepatotoxicity and hematologic toxicity were identified in nonclinical studies. In two animal species, a dose-dependent increase in liver enzymes was observed. Hematologic toxicity with some evidence for neutropenia was seen only at the highest dose evaluated. At the proposed dose, the safety margin for liver enzyme elevation is 4 times the targeted therapeutic dose and liver histopathology changes at 8 times the targeted therapeutic dose. At the proposed dose, the safety margin for hematologic events is 8 times the targeted therapeutic dose.

The MICs have a bimodal distribution with the wild type ranging from 0.06 – 1 mg/L and the non-wild type with MICs >4 mg/L. In a global survey of 850 recent *P. aeruginosa* isolates, 99% of isolates had an MIC $\leq$ 1 mg/L. In serial passage studies, the frequency of emergence of resistance is < 1 in 10^{10} organisms. The mechanism of resistance has not yet been determined. In animal models of infection, Drug X-1 demonstrated antibacterial activity in treating infections caused by *P. aeruginosa*. Dose fractionation studies in a hollow-fiber model and murine thigh and pneumonia infection models showed that the percent time that free-drug concentrations are above the MIC over a dose interval (%fT > MIC) is the PK/PD index associated with the bacterial killing effect.

Adequate drug concentrations were achieved in an ELF study in healthy volunteers. A Phase 2 proof of concept study conducted in patients with non-CF bronchiectasis showed that when administered as monotherapy to 10 patients, sputum CFU/g were reduced > 1 $\log_{10}$ in 9 of 10 subjects and by > 2 $\log_{10}$ in 4 of 10 subjects.

Clinical Development Program:

The following is a summary of the potential clinical development programs discussed at the workshop for Drug X-1.

Option 1: Non-inferiority Trial

The first and likely most feasible option of conducting a noninferiority (NI) trial was discussed in great detail, including sample sizes, NI margins, and the role of prior effective therapy and concomitant antibacterial therapy.

If X-1 is developed for HABP/VABP, it would need to be co-administered with a second antibacterial drug (e.g., ertapenem) to cover other potential pathogens, yet not obscure the treatment effect against *P. aeruginosa.* Ertapenem is approved for the treatment of community-acquired bacterial pneumonia (CABP) and not for HABP/VABP. It is not typically used clinically for treatment of HABP/VABP because its antibacterial spectrum does not include *P. aeruginosa*. As double-coverage for *P. aeruginosa* is a common clinical practice and ertapenem does not have a HABP/VABP indication, the clinical acceptability of X-1 plus ertapenem would need further consideration. Also, it is unclear if the ertapenem dosing regimen for CABP would be adequate for HABP/VABP. There was discussion about the clinical acceptability of ertapenem for the treatment of HABP/VABP and the need for further evaluation of the PK to assess if the approved dose of 1 gram per day will be adequate for the treatment of HABP/VABP. There was also discussion about confounding of the treatment effect of X-1 by other drugs that will be used to provide double-coverage for *P. aeruginosa*.

Workshop participants noted that from a feasibility standpoint, it may be possible to conduct such a trial with an NI margin equal to the M1 (20%). The estimated total sample size for such a trial ranges from 650 to1260 patients, depending on prevalence of *P. aeruginosa* of 20%-10%, in order to accrue 126 patients with *P. aeruginosa*.

Option 2: Superiority Trial at One Body Site or Across Multiple Body Sites

A second option considered was conducting a superiority trial at one body site or across multiple body sites. The trial would be designed to assess superiority against best available therapy in patients with infections due to *P. aeruginosa* resistant to currently available treatment options. The difficulty in conducting such a trial was discussed as it is likely that superiority will only be demonstrated if the *P. aeruginosa* is resistant to all available therapy. It was noted that resistance to both meropenem and amikacin is low and based on a recent surveillance study, the prevalence of such organisms is less than 1%. To find one patient with *P. aeruginosa* resistant to both meropenem and amikacin, one would need to enroll about 122 patients.

Option 3: Clinical Trials in Patient Population at Risk for Pseudomonas Infection
The third option presented was to study drug X-1 in patients with a higher likelihood of having *P. aeruginosa* infections such as cystic fibrosis or bronchiectasis. This option was not discussed in greater detail.

Option 4: Animal Rule
There was considerable discussion about potentially developing drug X-1 under the Animal Rule if interpretable human efficacy data cannot be obtained. The efficacy data from animals would be supplemented with clinical data from patients with a variety of infections caused by *P. aeruginosa* in one or more descriptive studies.

There was discussion about the potential use of validated external controls and about appropriate clinical use of drugs approved using any of these approaches. While some participants suggested that such a product might be used for empiric treatment, others indicated that they would reserve use of such products only for patients with few/no other options. Participants noted that labeling and stewardship considerations would need to be discussed for such a product.

Summary of the FDA Public Workshop held on March 1, 2017 (https://www.fda.gov/Drugs/NewsEvents/ucm534031.htm)

As a follow-up to the July 2016 workshop, we held a public workshop to further explore the current state of animal models for *A. baumannii* and *P. aeruginosa*.

The morning session of the workshop provided background on the unmet medical need for new antibacterial therapies to treat patients with infections caused by difficult to treat bacteria, highlighted lessons learned from the successful programs addressing biothreat agents such as *B. anthracis* and *Y. pestis* and included a discussion on the pathogenesis of infections due to *Pseudomonas* and *Acinetobacter* spp.

Examples of Clinical Development Programs
Examples from two clinical development programs one targeting *P. aeruginosa* and the other *A. baumannii* outlined the challenges with the clinical development of such products.

Example 1: Polyphor Ltd.
Polyphor Ltd. presented a summary of their product murepavadin (POL7080), a novel class of antibacterial drug that targets the outer membrane of *P. aeruginosa* including MDR/XDR strains. Activity of murepavadin has been demonstrated in murine lung infection models. The drug is bactericidal, demonstrates a low rate of resistance development, is not affected by surfactant and attains good ELF concentrations.

The Sponsor has conducted 6 phase 1 studies in healthy volunteers and two phase 2 studies, one each in non-cystic fibrosis bronchiectasis and VABP. In a small (n=12) phase 2 uncontrolled

VABP study in patients with confirmed *P. aeruginosa* infection, murepavadin was given in addition to standard of care; 10 patients were cured 7 days after EOT and 11/12 were alive at Day 28. Improvement in SOFA and CPIS scores and PaO2/FiO2 ratio was also observed. Based on the data accumulated so far, the safety profile appeared to be acceptable to proceed with further clinical development. Clinical dose selection was optimized based on target attainment using PK data from the Phase 1 studies and PK/PD target determined from animal models of infection.

The Sponsor discussed the difficulty in conducting a standard NI trial with a 10% NI margin (a total sample size of 3064 HABP/VABP patients based on a 22% incidence of *P. aeruginosa*) and the difficulty in demonstrating superiority. The Sponsor outlined their plan to conduct a multicenter randomized meropenem-controlled NI trial in patients with HABP/VABP due to suspected *P. aeruginosa* using 28-day all-cause mortality as the primary endpoint. The study population will be enriched by using rapid diagnostics to identify suspected cases. Concomitant use of ertapenem will be allowed in the study drug arm. The Sponsor noted that based on modeling work conducted, ertapenem 1 gram will provide adequate coverage against organisms identified in patients with VABP. The trial will also allow empiric dual coverage with addition of amikacin for up to 72 hours at the time of randomization. Overall, the Sponsor stated that such a study while challenging to implement, might be feasible.

Example 2: Entasis Therapeutics

Entasis Therapeutics discussed the program for their product ETX2514SUL, a novel non-β-lactam, β-lactamase inhibitor in combination with sulbactam to target *A. baumannii*. ETX2514 is an inhibitor of Class A, Class C, and Class D β-lactamases and restores the in vitro and in vivo activity of sulbactam against contemporary multi-drug resistant *A. baumannii*.

The Sponsor discussed the difficulties in identifying patients with *A. baumannii* infections as they represent ~2% of hospitalized gram-negative infections. These patients are often in the ICU and have co-morbidities.

The Sponsor discussed a study in ~ 200 patients with confirmed *A. baumannii* pulmonary/bloodstream infections. The primary endpoint in the trial could be 28-day all cause-mortality and the study will be designed using a 20% NI margin. Entasis anticipates that up to 60% of enrolled patients will have infection due to multi-drug resistant *A. baumannii.* The proposed study will allow for ≤48 hours of prior effective antibacterial therapy. In addition to the proposed phase 3 trial, the NDA package will include a strong microbiology package, evidence of in vivo efficacy in relevant animal models, robust demonstration of PK/PD parameters based on in vitro hollow fiber and in vivo animal models, and dose selection based on high probability of target attainment using robust modelling of preclinical and clinical data.

Entasis noted that such a study while not easy is potentially achievable.

Discussion of Animal Models

Based on the experience with developing animal models for biothreat agents such as anthrax, plague, and tularemia presenters noted the lengthy timelines in took to characterize and develop these models. The importance of a thorough histopathology assessment to characterize natural history and drug-disease interaction was also discussed.

P. aeruginosa was highlighted as an opportunistic pathogen, with healthy animals and humans being relatively resistant to infection. The pathogen displays immense adaptability and distinct pathogenic determinants depending on the site and source of the infection. Acute infections rarely disseminate and tend to stay localized. In chronic infections such as cystic fibrosis, there are changes in virulence factors and the ability to form biofilm. The International Pseudomonas consortium database provides access to >1500 well characterized strains with >900 draft genomes.

The complexities of *A. baumannii* including its diverse virulence/resistance characteristics were discussed. Infections caused by *A. baumannii* with blaOXA-23 genotype are associated with greater morbidity, longer duration of treatment and a protracted hospital course. In vitro assays for cell adherence, invasion and biofilm formation do not always correlate with virulence in vivo and do not appear to predict outcomes. Relative resistance of the murine models necessitates the use of either a very high inoculum (10^9), immunosuppression (neutropenic, diabetic), or mucosal irritation models raising questions regarding applicability of such models to clinical practice where patients lack similar risk factors. Rats appear to be less resistant than mice to *Acinetobacter* pulmonary and some skin infections. There was also discussion about non-mammalian models of *Acinetobacter* infections: *C. elegans*, zebrafish, and *Galleria mellonella* to further identify and characterize novel virulence factors and mechanisms of resistance.

The afternoon session focused on PK/PD considerations in animal model development and the specifics of individual animal models for *A. baumannii* and *P. aeruginosa* infections.

For PK/PD evaluation, mice can easily be used to assess activity generally based on a bacterial burden endpoint and PD parameters using a variety of models such as soft tissue, sepsis or lung infection. Outcomes in these models have generally correlated with clinical outcomes in patients. In these studies, different strains and clinical isolates with various MICs are usually tested. Limitations of the murine pneumonia model include variable susceptibility to human pathogens due to differences in lung anatomy/physiology, pattern recognition receptors, antimicrobial secretions, fewer neutrophils, lack of defensins, in addition to potential differences in alveolar macrophage and ELF penetration.

A neutropenic murine model of pulmonary *P. aeruginosa* infection developed to utilize clinically relevant inocula was discussed. In this model, clinically relevant endpoints of hypothermia, bradycardia, hypoxemia and disorientation are predictive of imminent mortality. Target organ bacterial burden along with dissemination rates were also discussed as being used to evaluate disease progression and response to treatment. This model is amenable to testing strains with variable susceptibility profiles, antibacterial drugs via different routes of administration, drugs in combination and host targeted biologics.

A. baumannii pulmonary and wound infection models presented utilized recent clinically relevant naturally competent MDR/XDR strains with well-established genetically identifiable virulence factors that are able to cause similar infections in various animal models and respond to positive control antibacterial drugs. The AB5075 strain of *A. baumannii* is highly lethal in *G. mallonella* and in the neutropenic murine model of pneumonia, achieves high burden in the lung tissue and has a high propensity for dissemination with a clear dose-response to a positive antibacterial control – rifampin. Murine and porcine models of wound infection were also discussed.

A rabbit model of pulmonary (HABP/VABP/septic shock) *P. aeruginosa* (Pa3077 +exotoxin strain) infection was discussed that may more closely replicate the human disease. The rabbit is the closest species after NHP to humans with respect to the inoculum necessary to produce clinical disease. Continuous ventilation with clinical hematology, chemistry, ECG, temperature, blood gas and culture monitoring allows for replicating the ICU setting. Mortality in this model appears to be related to respiratory failure or septic shock/ multi-organ failure.

A ventilated pig model of *P. aeruginosa* pneumonia was also discussed. This model is closer in anatomy/physiology as well as in disease pathogenesis (aspiration of oral secretions with gravity dependent dissemination), clinical course of the disease (lack of hemodynamic instability), and pathology to humans compared to small animals and provides advantages over the NHP model of VABP from a cost/animal availability standpoint. In this model, animals are sedated, paralyzed, and ventilated for 4-8 h prior to inoculation with *P. aeruginosa* (ATCC 27853) and are hemodynamically monitored. VABP is confirmed according to a histological injury score corresponding to a quantitative lobar (RLL, RML, LLL, but not RUL) culture of >3 log cfu/g.

Panel Discussion

Key points brought up during the panel discussion include:

1. Well characterized animal models similar to that of African Green Monkey for plague are difficult to develop for *P. aeruginosa* and *A. baumannii* because of differences in intrinsic degree of virulence of the pathogen and susceptibility of the host.

2. It is important that results be consistent across the spectrum of animal models, mammal vs. non-mammal, neutropenic vs immune competent, small vs. large using clinically relevant bacterial strains.
3. It might be useful to use standard benchmarks to prove that the model is sensitive, e.g. positive and negative controls using antibacterial drugs that are known to be efficacious and those that have been shown to be ineffective/less effective at a particular site of infection.
4. Histopathological assessments and monitoring disease biomarkers throughout the course of the disease and recovery may provide some useful information.
5. Small animal models could potentially be used for screening for activity and large animal models could be used to mimic the physiologic derangements seen in patients.
6. As there is a fair bit of variability in findings with different bacterial strains in any given model, it is important to study different strains and clinical isolates that are appropriate for the particular animal model. Those with a well described pedigree in animal models are preferred.
7. Overall, it was recognized that while no single animal model might be best suited to study infections caused by these organisms, 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 such therapeutic agents.

Regulatory Considerations

Potential development pathways that we have considered to support approval of such products and their limitations are discussed below:

Approval based on a small clinical trial dataset

Noninferiority Trials:
We have considered a single NI trial using a wider NI margin than would typically be used for a standard development program. For example, for HABP/VABP, the NI margin is 10% for standard development programs and 12.5% for products that address an unmet need. If a trial is limited to a single species of interest, the size of a NI margin may be even larger, provided that the data supporting NI margin justification are available. In this case, it may be acceptable to choose an NI margin equal to the estimated treatment effect.

The main advantage of this approach is that such a clinical trial, although difficult to conduct, might be feasible. However, there may be greater uncertainty in the treatment effect with such programs. Also, 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.

Superiority trials:
It might be feasible to conduct superiority trials for the first one or two products that are being developed as it might be possible to demonstrate superiority over current SOC. The ability to demonstrate superiority is often time-limited and as new therapeutic options become available, SOC could change and this may alter or remove the opportunity to show superiority. As planning for superiority is risky given that the trial may become infeasible and/or unethical at the point a new SOC replaces the less than adequate comparator treatment, Sponsors are generally not willing to take this approach.

Approval based on the Animal Rule (21 CFR 314.600):
The following criteria must be met for evidence from animal studies to provide substantial evidence of effectiveness:

- There is a reasonably well-understood pathophysiological mechanism of toxicity of the substance and its prevention or substantial reduction by the product;
- 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 species that represents a sufficiently well-characterized animal model for predicting the response in humans;
- The animal study endpoint is clearly related to the desired endpoint in humans, generally the enhancement of survival or prevention or major morbidity; and

- The data or information on the PK and PD of the product or other relevant data or information, in humans and animals, allows selection of an effective dose in humans.

Additional work will need to be done to identify the appropriate animal models for the infection type being studied as none of the currently available models have been developed for this purpose. Currently, animal models are used to provide evidence of the antibacterial activity of a drug, typically using an endpoint of reduction in bacterial load and to evaluate PK/PD characteristics of the drug. In contrast, animal studies supporting Animal Rule approvals have generally assessed effect on mortality. If the product is approved under the Animal Rule clinical data from humans will be available to provide safety information and some data will be available on clinical outcomes (although it may not be very informative). For approval based on the Animal Rule, the comparison of PK data, including the concentrations in infection sites as well as in plasma, between animals and humans is critical to determine an effective dosing regimen in humans. Furthermore, following an Animal Rule approval, the design and characteristics of a post marketing study to verify and describe the drug's clinical benefit would need additional discussion.

Use of surrogate endpoints for Subpart H approval (21 U.S.C. 356(c); 21 CFR 314.500 et seq.):

a. We have considered proposals regarding the use of microbiologic endpoint as a surrogate. As noted below, at this time we do not consider microbiologic endpoints as appropriate surrogate endpoints for acute infectious diseases:
   - The timing of the microbiologic endpoint is usually close to or concurrent with the clinical endpoint, unlike tuberculosis where there is a lag of a few months between assessment of microbiologic and clinical outcomes.
   - For most infectious disease indications, the clinical endpoint is usually within 28 days of randomization and hence the clinical outcome is known in a reasonable timeframe.
   - It is possible to have discordance between microbiologic outcome and clinical outcome. For example, bacterial culture can be negative when assessed at an earlier time point, e.g. days 10-14 and patient is not alive by day 28.
   - Treatment effects on microbiologic endpoints have not necessarily translated to effects on clinical outcomes. For instance, in a recently published randomized trial comparing colistin plus rifampicin versus colistin in 210 patients with life-threatening multidrug-resistant *A. baumannii* infections, the difference in eradication rates (61% versus 45%, p=0.03) did not lead to a difference in the primary endpoint of 30-day survival (57% versus 57%, p=0.95)[5].

[5] Durante-Mangoni, Signoriello G et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant *Acinetobacter baumannii*: a multicenter, randomized clinical trial. Clin Infect Dis. 2013 Aug; 57(3):349-58.

- For many infections, such as HABP/VABP, often the microbiologic outcome is presumed eradication if the patient is cured. Cultures are typically not very helpful or obtained if the patient is clinically improved/cured.
- Similar to clinical endpoints, microbiological endpoints can also be confounded by prior/concomitant therapy.

b. We have considered the use of concentrations of the test drug in plasma and/or infection sites such as epithelial lining fluid, cerebrospinal fluid as a surrogate and note the following limitations:

While a thorough understanding regarding drug concentrations in infection sites could provide supportive evidence for the smaller clinical data package, it may not be possible to fully rely on concentrations of the test drug in plasma and/or infection sites as a surrogate endpoint. Some scientific issues that will need further discussion are:

- Clear exposure-response relationship between free drug concentrations in infection sites and activity (reduction in bacterial loads or survival) in appropriate animal model(s).
- Achieving free drug concentrations in infection sites that exceed a certain MIC value do not necessarily translate to a clinical benefit. MIC values can vary significantly depending on test conditions, for example use of polysorbate, iron concentrations in the media, divalent cations, pH, inoculum density, and incubation conditions.
- Potential differences in drug concentrations in infection sites as well as in plasma between healthy volunteers and infected patients.
- Differences in pathophysiology of infection (e.g., differences in immune system and formation of biofilm) between animals and humans.

If approval under subpart H is considered using plasma/infection site drug concentrations, further discussion will be needed regarding the design of the trial in which the efficacy of the drug based on the surrogate will be assessed as well as the design of the post marketing trial to verify and confirm the drug's clinical benefit.

Limited Population Pathway

We also note that section 3042 of the 21st Century Cures Act (Pub. L. 114-255) establishes a limited population pathway for certain antibacterial and antifungal drugs (LPAD) that are intended to treat serious or life-threatening infections in limited populations of patients with unmet needs. Drug products that target a single bacterial species that infrequently causes infections may be candidates for LPAD because of the inherently limited population of patients for whom the drug is intended and greater uncertainty regarding the benefit risk profile of the drug that may follow from the development approaches described above. Labeling for LPAD

products will include the term “Limited Population” in a prominent manner and the statement “this drug is indicated for use in a limited and specific population of patients.”

Topics for Advisory Committee Discussion:

a. Please discuss the pros and cons of the different clinical development options presented and any additional suggestions you might have for developing such products.

b. While every effort will be made to perform human clinical trials, performing clinical trials of such drugs will be challenging and data collected may not be interpretable or be very limited. In this situation, animal models of serious bacterial infections may provide useful information to assess the activity and efficacy of the drug. In such a situation, please discuss:

   i. The types of information from the animal models that you think might be useful to assess efficacy of the investigational agent, such as types of animal models and appropriate endpoints.
   ii. The clinical use of products where efficacy was demonstrated in animal models of infection.
   iii. Types of clinical data that would be helpful in addition to the efficacy data from animal models of infection.