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Clinical pharmacokinetic–pharmacodynamic analyses: a critical element for developing antibacterial agents

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In the current of era of developing antibacterial agents, including those for unmet medical need, Sponsors are required to submit a robust pre-clinical pharmacokinetic–pharmacodynamic (PK–PD) data package in exchange for limited clinical data. However, the clinical data package also needs to be as robust as possible. The clinical data package needs to include the Phase 1 pharmacokinetic (PK) studies conducted in the target patient populations and special populations. Additionally, PK data need to be collected from all patients enrolled in the pivotal trial(s). Such data are critical to confirm adequate drug exposures relative to non-clinical PK–PD targets for efficacy, explain unexpected clinical failures in individuals or groups of patients, and evaluate exposure–response relationships for safety.

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Introduction

Over the last several decades, we have learned the value of using pharmacokinetics–pharmacodynamics (PK–PD) principles to develop antibacterial agents. This paradigm, which starts early in development with the conduct of pre-clinical PK–PD studies, utilizes such data with Phase 1 PK data and Monte Carlo simulation to forecast dose. The collection of PK data from patients during clinical trials has allowed for exposure–response analyses for efficacy and safety to be conducted. The results of such analyses for efficacy have allowed for confirmation of predictions for dose made early in development. While this approach, based on typical clinical trial data packages consisting of Phase 2 and 3 study data, has been successful for investigating exposure–response relationships for efficacy and safety, it is not feasible to collect such data when developing antibacterial agents to treat patients with resistant bacterial infections.

As evidenced by the recent experiences for Phase 3 evaluations of plazomicin and meropenem-vaborbactam for patients with serious infections due to carbapenem-resistant Enterobacteriaceae (CRE), the enrollment of even a limited number of patients can take many years. Such trials, although difficult to complete, are needed in the interest of public health [1••]. For both drug development programs, the completion of concurrent Phase 3 trials in patients with complicated urinary tract infections in the setting of pathogens with usual drug resistance (UDR) was, however, accomplished in less time. Thus, to ensure that antibacterial agents to treat patients with bacterial infections arising from resistant pathogens can be made available in a timely manner, regulators have shown a willingness to exchange certainty provided by a robust clinical data package with that provided by robust pre-clinical PK–PD and Phase 1 study data packages in combination with a limited clinical data package.

Herein, the pre-requisites for pre-clinical and clinical data packages for the development of antibacterial agents for the treatment of patients with resistant infections will be reviewed. The value of typical Phase 2 study designs will be considered in the context of the current paradigm for developing antibacterial agents for indications that include pathogens with UDR and for which it is not difficult to enroll patients. Expected findings from PK–PD analyses for efficacy based on Phase 2 and 3 data for such indications will also be discussed. Lastly, the opportunities available to conduct exposure–response analyses for safety based on clinical data packages will be addressed.

Recommendations for data packages for antibacterial agents for resistant pathogens

Within the last decade, specific efforts have been put in place to foster the development of antibacterial agents. These efforts have included changing legislature, increasing the availability of funding, and providing regulatory guidance. In United States of America (USA), the Generating Antibiotic Incentives Now (GAIN) Act, which provides an additional exclusivity period of five years during which certain antibiotics that treat serious or life-threatening infections can be sold without generic competition, was signed into law in 2010 [2]. Agents that qualify for GAIN provisions also receive fast track and priority review status and undergo an expedited regulatory approval process with the USA Food and Drug

Administration (US FDA). Additionally, the 21st Century Cures Act (Cures Act), signed into law on December 13, 2016, is designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently. Among the provisions described, those under Title III, Subtitle E, and Section 3042, for Antimicrobial Innovation and Stewardship establish a Limited Population Antibacterial Drug (LPAD) regulatory pathway for antibacterial agents that will be used to treat patients with serious or life-threatening infections for which there are unmet medical needs [3]. This builds upon the US FDA 2013 draft guidance on developing antibacterial agents for patients with unmet need [4], which was recently finalized [5], and thereby, provides a mechanism for smaller clinical trials for such agents. Separate US FDA guidance regarding LPAD is forthcoming.

With regard to funding, Biomedical Advanced Research and Development Authority (BARDA), within the Office of the Assistant Secretary for Preparedness and Response, established a Broad Spectrum Antimicrobials (BSA) Program in April 2010 to develop novel antibacterial and antiviral drugs to treat or prevent diseases caused by biological threats. Like the GAIN act, the public health threat of antimicrobial resistance is an important focus of the BSA program, which provides non-dilutive funding to support product development and augment existing capital raised from investors.

From a regulatory standpoint, updated US FDA guidance for a number of indications, including hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, serves to increase the certainty around development pathways for antibacterial agents in the USA [5–10]. However, at present, the most urgent need is for regulatory pathways to develop antibacterial agents to treat patients with resistant Gram-negative pathogens, including narrow-spectrum agents targeting resistant *Pseudomonas aeruginosa* and *Acinetobacter* and *Klebsiella* species. To this end, the US FDA convened a workshop in July 2016 to address the challenges and emphasize the need for such agents [11]. As a follow up, workshop participants, on behalf of the Infectious Diseases Society of America, issued a white paper summarizing approaches for clinical trial design and data packages that should be considered in support of developing agents to treat patients with infections caused by a single pathogen and/or in patient populations with the greatest unmet medical need [12••].

An important concept of the above-described workshop and white paper [11,12••] is the level of certainty associated with different types of data. For indications involving relatively susceptible pathogens and for which a comparator agent can be studied, certainty has traditionally come in the form of multiple robust clinical studies that are powered to demonstrate non-inferiority and large enough to detect safety signals. The value of non-inferiority trials in the setting of UDR has been previously reviewed [1••]. However, clinical studies to evaluate antibacterial agents for the treatment of patients with highly resistant infections are not feasible to conduct in a reasonable timeframe. Patients with highly resistant infections are infrequent and when encountered, critically ill, and thus, challenging to enroll [12••].

In this circumstance, the certainty that is lost by not having a large clinical trial database can be exchanged for the certainty that can be achieved by building and leveraging robust pre-clinical PK–PD and Phase 1 PK data packages with smaller clinical datasets. The former allows for greater certainty with regard to the priors that are used for dose selection. The latter allows for greater certainty that targeted drug exposures can be achieved in applicable patient populations. A robust pre-clinical PK–PD data package must include data that both identify the PK–PD index associated with efficacy and quantify the magnitude of that index required to achieve relevant reductions in bacterial burden. These determinations should be based on a diverse collection of isolates. The challenge panel for dose-ranging studies should include a number of clinical isolates sufficient to characterize the variability associated with a given PK–PD target. Additionally, the panel should include isolates with MIC values spanning a clinically relevant range and expressing applicable resistant determinants. Given that good concordance has been observed between the magnitudes of non-clinical PK–PD indices required to achieve certain levels of bacterial reduction and clinical PK–PD indices associated with successful response [13••], such pre-clinical PK–PD data are key inputs for dose selection. The inclusion of resistant bacterial isolates in such evaluations will increase the relevance of any inferences made using these data.

While *in vitro* chemostat and *in vivo* infection models have proven to be effective systems that can be used to conduct dose-fractionation and dose-ranging studies, these systems are limited by the duration of studies that can be undertaken. To answer questions about how dosing regimens should be administered for infections requiring longer durations of treatment or the magnitude of the PK–PD index associated with the prevention of resistance emergence, studies utilizing an *in vitro* hollow fiber infection model should be undertaken. As has been discussed by others, it is important to use the most appropriate infection model to answer a given question [14••,15••]. The evaluation of select isolates across infection models and even across independent laboratories will provide important confirmatory evidence. Given the comparatively lower cost of studying an isolate relative to a patient, the certainty afforded by a robust pre-clinical package executed in this manner is cost-effective.