De-Risking Antibiotic Drug Development with PK-PD

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The Importance of PK-PD

Pharmacometrics, which includes the science of pharmacokinetics-pharmacodynamics (PK-PD), is one of the most commonly misunderstood, misused, and under-appreciated resources available to drug developers. In the past PK-PD was an afterthought, but today it is required by regulators – and here’s why.

Know the Key Issues: Historically, the overwhelming majority of early-stage failures for anti-infective drugs have been attributed to disappointing PK characteristics (FIGURE 1). An evaluation across all therapeutic classes showed that approximately 50 to 85% of early- or late-stage drug failures were due to unsatisfactory efficacy or safety. Since insufficient efficacy primarily relates to issues of poor dose selection, an understanding of population PK modeling and pre-clinical data is an important place to start. There are numerous other factors to consider—spanning the microbiologic, pharmacometric, and clinical strata. Some of these include:

- The evaluation of pathogen susceptibility distributions
- An assessment of the effects of patient covariates on drug disposition
- Determining the appropriateness of your chosen dosing regimen: amount, frequency, duration

De-risk Your Program: PK-PD analyses enable the evaluation of the safety and efficacy of your antimicrobial – past, present and future. Lessons from past successes and failures can teach us how to move forward with present and future programs. For example, an assessment of the relationship between the probability of PK-PD target attainment for antibacterial dosing regimens and the likelihood of regulatory approval by the United States Food and Drug Administration (FDA) demonstrated that

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FIGURE 1: Reasons for early-stage failures of anti-infective drugs

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as the probability of PK-PD target attainment for a given dosing regimen increased, so too did the probability of regulatory approval1 (FIGURE 2). Among the programs evaluated achieving at least 90% percent probability of PK-PD target attainment, 88% received FDA approval.

**Take Initiative:** Being proactive is key to maximizing the benefits gained through the application of PK-PD. The use of PK-PD early in drug development informs decision-making, safeguarding the program’s well-being. For instance, you might wonder, “How do I select safe and effective doses for Phase 2 trials?” The answer is to first use drug concentration-time data from healthy human subjects to develop a population PK model. This model, in conjunction with a pre-clinical PK-PD target associated with efficacy, will allow you to identify dosing regimens that achieve efficacious drug exposures in patients. So what’s the end result? Reducing your risk of conducting a lengthy and expensive clinical trial only to discover in the end that you selected sub-therapeutic or toxic doses at the onset.

**Generate Insights:** Well-orchestrated PK-PD analyses ensure patient safety and hold the potential to generate invaluable knowledge. Take the case of oritavancin for example. This drug was initially developed for once daily administration. Three separate pharma companies took this approach and achieved mixed results—but eventually the importance of oritavancin’s concentration-dependent killing was recognized. This fact, coupled with the drug’s extremely long half-life, led to the insight that a single large dose could be administered in lieu of smaller daily doses. Oritavancin went on to become the first antibiotic approved with a single-dose regimen for acute bacterial skin and skin structure infections (ABSSSI).

### In Vitro Susceptibility Data

**Characterize the Pathogen Population:** Before selecting a dosing regimen, you need to know more than just your antimicrobial’s spectrum of activity. Without knowing the width of the MIC distribution and number

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of resistance determinants for the pathogen(s) of interest, it is possible to get to late stage development only to discover that isolates in a large and diverse patient population are less susceptible than expected. A large, contemporary *in vitro* surveillance study is needed to capture the presence and frequency of relevant antimicrobial-resistance determinants in addition to defining the MIC distribution.

**Determine What is Relevant:** Ensuring that the isolates studied are representative of those that will be studied clinically is paramount. Context is key. For instance, patients from the intensive care unit often have extensive prior antimicrobial histories. Isolates obtained from these patients tend to be less drug-susceptible than those from other patients. Such was the case for tigecycline. An analysis of patients enrolled in a Phase 3 clinical trial revealed that the minimum concentrations of tigecycline required to inhibit 90% of isolates (MIC$_{90}$) in patients with hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) were 1 and 16 mg/L, respectively (FIGURE 3). However, evaluating these data more simplistically as one homogeneous population tells a different story entirely. This approach yields an MIC$_{90}$ of 2 mg/L. The latter approach leads to a gross underestimation of pathogen susceptibilities within the VABP patient population, which greatly increases the chance of witnessing treatment failures. Such was the case in the tigecycline drug development program. Thus, designing your *in vitro* surveillance study to match the indication being

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sought improves the relevance of your data, consequently increasing the likelihood of regulatory success.

Pre-clinical Infection Models

Make Informed Decisions: There exists a rich variety of PK-PD models effective in providing support when deciding upon a dosing regimen, including in vitro one-compartment (chemostat) and hollow fiber infection models as well as a variety of in vivo infection models. These models can be leveraged to answer overlapping aspects of the “how much, how often and for what duration” dosing questions, but they all have their unique strengths and weaknesses.

Be Efficient: While understanding the strengths and weaknesses inherent to each pre-clinical infection model is important, this merely lays the foundation for success. The true finesse is knowing the appropriate mix and timing with which to implement these models. Adeptly using and ap-
plying pre-clinical models will allow you to fully understand the PK-PD profiles of your antimicrobial, which in turn, can lead to the selection of the optimal dosing regimen for your agent. Ultimately, the knowledge generated from pre-clinical infection models will assist in reducing the risks you face and improve your likelihood of attaining regulatory approval.

Population Pharmacokinetics

**Identify Nuances in Drug Disposition:** Understanding the PK properties of your drug, such as clearance and disposition, and how these are impacted by various patient factors is key to your success. Consider this: non-linear and non-stationary PK can lead to higher (or lower) than expected concentrations of your drug in patients with respect to dose and time, respectively. These anomalies in PK may increase the likelihood of witnessing sub-therapeutic dosing and drug induced toxicities in clinical trials, compromising the wellbeing of your drug development program. Despite these pitfalls, population PK modeling allows you to develop an optimal dosing regimen and to extrapolate pre-clinical findings to clinical practice, de-risking your drug development program.

**Balance Efficacy and Toxicity:** Treading the line between toxicity and efficacy is challenging. The extent to which your drug concentrates in plasma and tissue can differ greatly from healthy subjects to patients with serious comorbidities and even from one patient to another for a given indication (FIGURE 4). Understanding the magnitude and basis of this variability becomes especially important if you plan to develop a single dosing regimen for patients with different indications or if your drug has a narrow therapeutic index. Fortunately, by employing a population approach to PK modeling, you can determine the dose placing the maximum number of individuals within the therapeutic window. Should this regimen still insufficiently minimize patient risk, you can develop dosing regimens tailored to specific patient groups based on individual covariates determined to affect the PK of your drug.
Perform the Right Clinical Studies: Covariate analyses can be put to use to better inform the clinical development decision-making process. By understanding the factors affecting the PK of your drug using data from existing clinical studies, you can maximize the information provided by these studies and potentially eliminate the execution of additional studies. As a for instance, let’s say you suspect that a patient’s weight impacts your drug’s PK. Your next step would be to pool data from across Phase 1, 2 and 3 studies performed to date. Assuming there is sufficient variability in weight among the pooled patients in these studies, you can evaluate weight as a covariate in your final population PK model and characterize how weight impacts the disposition of your drug. If weight has little or no impact on your drug’s PK, you will have avoided the need to perform a Phase 1 study in obese subjects. However, in the event that the effect of weight on your drug’s PK is impressive, you can then consider if an additional study in obese subjects is warranted. In either scenario, this approach will provide important information and an objective basis to decide if more resources need to be committed to gathering additional clinical data.

Refine Your Model: Basing your population PK model on as little as one Phase 1 study can generate vital information. Your initial model will aid

in early dosing regimen selection by simulating distributions of expected drug exposures to estimate efficacy and toxicity. This model can continue to be refined by incorporating new data as they become available. Doing so will provide decision support and enable you to ask and answer questions as they arise throughout development. Developing a population PK model early and updating it often allows you to generate knowledge about your drug and adapt your strategy to the obstacles you face.

**Exposure-response Relationships**

**Validate Prior Decisions and Discoveries:** The evaluation of exposure-response relationships for an antimicrobial agent using data from Phase 2 and 3 studies provides a number of opportunities.

- Information derived from such analyses allows us to learn and understand why certain patients fail therapy while others are successfully treated.

- These data also enable the evaluation of relationships between exposure and the probability of safety events, which are used to determine whether such adverse events are predictable rather than idiosyncratic.

  - Using exposure-response relationships for efficacy and/or safety, identified based on clinical data ([FIGURE 5](#)), provides a mechanism for determining efficacious and safe dosing regimens.

  - These data can also be used to **confirm** predictions made for dosing regimens earlier in development – and ultimately, this iterative process aids in safeguarding your regulatory pathway, enabling you to **succeed**.

**Determine Optimal Dosing:** Brilacidin is an antimicrobial agent which mimics the structure and function of host defense proteins. Exposure-response analyses were conducted for this agent to evaluate dosing regi-
mens for future Phase 3 studies in patients with ABSSSI. Results of these analyses demonstrated that as brilacidin exposure increased, so did the probabilities of a successful clinical response and reduction in lesion size. In addition, significant, exposure-related increases in systolic blood pressure and the occurrence of numbness and tingling events were identified. These data enabled developers to pinpoint an optimal dose, which balanced the needs for high efficacy and minimal risk of these safety events, thereby maximizing the benefit provided to patients and likelihood of regulatory success.

**FIGURE 5:** Predicting an ever shrinking therapeutic window in the face of increasing microbial resistance.

![Graph showing AUC and Probability against MIC values](image)

**Susceptibility Breakpoints**

**Manage Patient Variability:** The selection of appropriate susceptibility breakpoints is more science than art—drawing upon microbiologic, pharmacometric, and clinical data to construct a set of breakpoints which identify susceptible, intermediate, and resistant organisms (FIGURE 6). The first step in this process is to admit that not all patients are equal, and that variability is to be expected. To begin describing this variability, you must

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initially collect PK data from patients similar to your targeted population. Using these data, you can then rely upon population PK modeling to provide parameter estimates to describe the disposition of your drug across a population of patients. But these estimates alone are not going to provide the answers you seek – they must be applied through Monte Carlo Simulation to generate a distribution of drug exposures representing those expected in your target patient population.

Apply Your Findings: Without appropriate application, the exposure data you have generated won’t be very helpful. This is achieved through the integration of PK and PD, yielding PK-PD indices of efficacy (e.g., AUC:MIC, Cmax:MIC, and %T>MIC) and target magnitudes. Integrating the population PK-derived parameter estimates and PK-PD targets through Monte Carlo simulation, you can calculate the percent probability of PK-PD target attainment for your drug’s dosing regimen at each MIC dilution. To take it a step further, this output can be plotted over contemporary MIC distribution data for your target pathogen. This visual provides a better understanding of your drug and allows more informed decision-making when assessing susceptibility breakpoints.

Be Critical: The susceptibility breakpoints you select will ultimately be used to justify the dosing regimen you intend to take into Phase 3 trials, which is why they will first need to be evaluated with a critical eye.
■ Does my susceptible breakpoint capture the MIC₉₀ of the MIC distribution utilized, and is this distribution representative of the population of a given pathogen that I want my drug to cover?
■ Does my drug achieve a high probability of PK-PD target attainment at the susceptible breakpoint and, ideally, at least one dilution higher?
■ How does my susceptibility breakpoint hold up when accounting for variability in pathogen resistance?

Knowing the answers to these questions will provide the basis for a strong dose justification document.

**Know the Road Ahead:** Determining appropriate susceptibility breakpoints is critical to the success of any drug development program since getting to market is only half the battle. Regulators and clinicians alike use susceptibility breakpoints to determine the utility of antimicrobials. So even if your agent obtains regulatory approval, it will need robust breakpoints in order to achieve use by prescribers and capture market share. Risk mitigation is the key objective and evaluating susceptibility breakpoints throughout clinical development is what keeps you cognizant of the marketability, and inevitable success, of your new drug candidate.