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PK/PD of Antimicrobial Agents: Get it right or expect a rough ride

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Both the FDA and EMA consider robust PK/PD data to be central to antibacterial drug development programmes [1, 2]. Whilst guidance documents are available, the exact scope of data needed is not clearly defined [3] which can result in a company's PK/PD data package being considered inadequate or can be problematic during the regulatory review process. In this article, we briefly discuss the goals of PK/PD assessment in the development of antimicrobial agents and look at some real-life, but anonymised, examples where the PK/PD package generated fell short of the regulator's expectations and the consequences this had for the antimicrobial agent.

Pharmacokinetics/Pharmacodynamics (PK/PD) is a quantitative approach to predict clinical efficacy based on both PK and PD data [4]. PK relates the administered dose of the agent with the concentrations seen in the body over time whilst PD is concerned with the magnitude and time course of the observed pharmacological effect. Antimicrobial agents differ from other drugs in that their PD effect is exerted on microbial pathogens rather than (ideally) any direct effect on human cells and tissues [5].

The discipline of PK/PD has been developing for several decades now and the evidence demonstrating that clinical outcomes can be predicted by non-clinical infection models is extensive [6]. Characterising the PK/PD relationship of new antimicrobial agents during development is important as this can contribute valuable information to the selection of a dose that will ensure clinical efficacy but is least likely to cause adverse effects or the emergence of resistant organisms [7]. Solid PK/PD data is even more critical when the new agent is being developed to treat drug-resistant bacterial species as demonstrating clinical efficacy is challenging due to the relative rarity of patients infected with target bacterial species [3].

Over the past 10 years, both the FDA and EMA have issued guidance enabling streamlined development programmes of agents for the treatment of infections with limited therapeutic options [1, 2, 8]. Both agencies expect the PK/PD data package to support and complement the clinical trial data and to justify the selected dose when granting an application for marketing authorisation [5, 7]. In addition, PK/PD data are critical for setting appropriate clinical breakpoints [9] which are published by the Clinical and Laboratory Standards Institute (CLSI) and the US Committee on Antimicrobial Susceptibility Testing (USCAST) in the US and by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in Europe.

Best practices for assessing PK/PD during the development of antibacterial agents were identified in 2017, at a workshop organised by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH) [6]. To be robust, the non-clinical PK/PD package should (a) quantify the PK/PD targets for efficacy in ideally two experimental systems, including *in vitro* and *in vivo* infection models, (b) be based on bacterial isolates which have a range of susceptibilities (MICs) and resistance mechanisms expected clinically, (c) be derived from a sample size sufficient to assess the variability in the magnitude of the targets, and (d) be externally consistent and reproducible, i.e., ideally based on data generated by two or more groups of investigators [3, 6].

The recommendations from the NIAID/NIH workshop are extremely useful to companies developing new antimicrobials, but they are the opinions of the workshop participants and do not constitute regulatory guidance. Whilst regulatory agency guidance documents are available, they do not clearly define the exact scope of data needed [3]. Consequently, some companies have generated PK/PD data packages that have been considered inadequate or problematic by the regulators during the review process. Sometimes this does not cause any major problem but in other cases has required considerable effort to alleviate the regulators' concerns, from re-analyses of data and provision of a convincing position piece to the need to conduct additional studies which can delay approval. The following illustrates some of the problems that tranScrip has come across which either resulted in or may have resulted in a PK/PD package that fell short of the regulator's expectations:

- A first-in-class agent with potent activity against multi-drug resistant pathogens had PK/PD target values that showed extremely broad inter-strain variability. As a consequence, the regulatory agency requested that probabilities of target attainment (PTA) were re-calculated using the 95-percentile value rather than the mean or median value that is normally used. This resulted in a considerable decrease in the PTA and, consequently, the potential clinical breakpoint MIC decreased from a >MIC_{90} value to a <MIC_{50} value (i.e., the breakpoint bisected the wild-type MIC distribution). The company needed external support to conduct a close review of the various studies, of which some were found to be sub-optimal, and additional studies using a second, hollow-fibre infection model (HFIM) had to be conducted, to clarify the appropriate PK/PD target. This resulted in additional expenditure for the company.
- A new member of a well-established antimicrobial class had a modified mode of action resulting in *in vitro* activity some ≥ 64-fold higher than that for existing class members. PK/PD targets were found to be 5-fold lower than that expected for this antimicrobial class which, as the company believed, was a consequence of the enhanced activity. PTA analyses suggested that this new drug, at the chosen dose, would cover isolates considered "resistant" to the other members of the class.

However, because the PK/PD magnitudes were not consistent with that expected for this antimicrobial class, the PK/PD assessment was relegated during the setting of clinical breakpoints, and, without clinical efficacy data against "resistant" isolates, the breakpoints granted were lower than requested and did not cover isolates that were considered resistant to other members of this antimicrobial class. The consequence of the lower breakpoints meant that the company's ability to differentiate their product from competitors was greatly reduced.

- Another first-in-class agent with potent *in vitro* activity against target pathogens, and excellent *in vivo* efficacy in appropriate animal infection models, had PTA values that suggested low likelihood of efficacy at the proposed clinical dose using PK/PD target values derived from the conventional endpoints, net antimicrobial stasis and 1-$\log_{10}$ CFU reduction from baseline. Application of non-conventional endpoints such ED_{25} and ED_{50} resulted in improved PTAs which were more aligned to the effectiveness seen in the animal models. A Phase 2 clinical study is ongoing and will provide additional information that will be useful in confirming whether or not PK/PD assessment for this novel agent requires the use of a non-conventional approach.
- A novel member of an established antimicrobial class was shown to be 99% protein bound to human serum, and the PK/PD targets were somewhat lower than that seen with other members of the class. As limited protein binding studies had been conducted by the company and, because protein binding of antimicrobial agents can be confounded by factors such as temperature, pH, electrolytes and concentration-dependent binding, there was some concern that the PK/PD targets for efficacy were under-estimated. For example, if the protein binding value was, in reality, 97%, then this would result in a 200% difference in the free fraction [4] and use of the "artificially elevated" protein binding value would result in an artificially low PK/PD target value and over-estimate the PTA. The consequence of this error could be that the dose chosen for clinical studies may be too low, leading to a failed clinical study. Additional protein binding studies were performed and confirmed the high protein binding value for this new agent and the chosen dose was subsequently shown to be clinically effective.

Summary

In summary, PK/PD assessments are critical in the development of antimicrobial agents. Whilst guidelines are available, there is a lack of well-defined requirements, which can result in a PK/PD package that is sub-optimal. Submission of such a package for regulatory review could result in the need for considerable effort to be made to resolve queries during the regulatory review process, including additional studies to be conducted with a subsequent delay in approval. As a worst case, poor PK/PD assessment could lead to the selection of an ineffective clinical dose.

Contact Us

tranScrip has considerable experience in developing antimicrobial agents and assessing PK/PD packages.

If you would like assistance with ensuring that your PK/PD package is optimal, please contact us on 0118 963 7846 or email us info@transcrip-partners.com.

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