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Ensuring quality pharmacokinetic analyses in antimicrobial drug development programs

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Pharmacokinetic studies and analyses can be expensive, time consuming, and labor intensive. However, it is crucial to understand that much of what happens in antimicrobial drug development, such as dose-selection and clinical study design, can be optimized with a strong understanding of the underlying pharmacokinetics of an agent. In this way, pharmacokinetics forms the bedrock of a pharmacometric approach to antimicrobial development. Thus, pharmacokinetic analyses must be considered an integral part of a drug's development strategy and studies must be planned and designed accordingly. This paper provides a brief overview of pharmacokinetic analysis methods, including best practices and their use in the context of a drug development program. In addition we will conclude with an overview of proper design and conduct of pharmacokinetic studies to optimize their use in evaluating clinical study data.

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Introduction

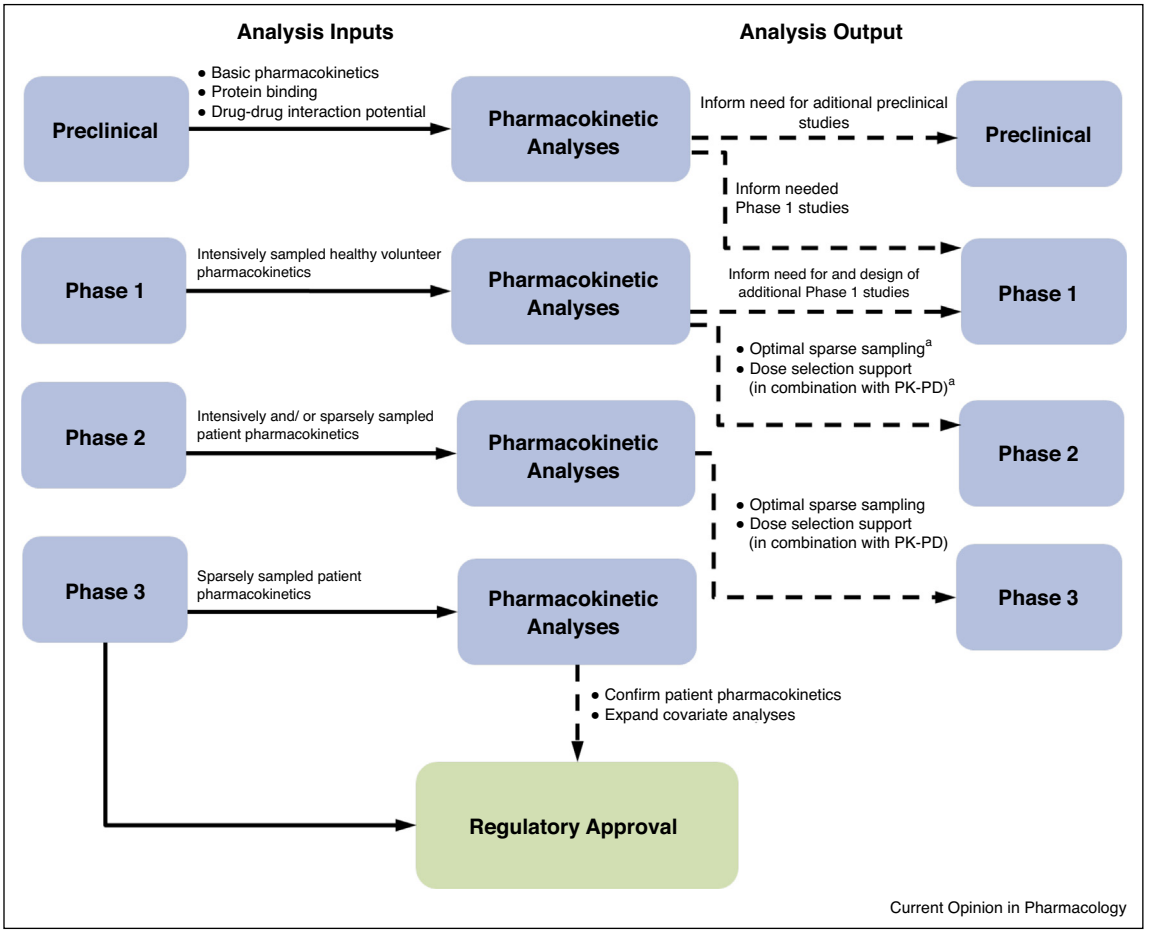
Historically, approximately 90% of early-stage antimicrobial drug development failures have been attributed to poor pharmacokinetic characteristics of the investigational agent [1], factors which often render one unable to select doses which balance the competing needs for low toxicity and high efficacy. Conversely, late-stage programs most often fail due to inadequate safety or efficacy findings, and these can often be tied to poor dose selection in clinical studies [2]. This should make apparent the need to obtain a thorough understanding of a drug's pharmacokinetics at all stages of development in order to inform decisions made every step along the way. Pharmacokinetic analyses can be leveraged in a number of ways to answer questions and mitigate development risks. These might include the determination of whether a food effect is present and clinically relevant, predicting the likelihood of witnessing subtherapeutic exposures with doses planned for clinical study, or evaluating whether renal impairment influences the safety and efficacy of a given dose regimen. When utilized appropriately, pharmacokinetic analyses form the foundation of a pharmacometric approach that can be leveraged to greatly reduce the risk of program failure — particularly those in the antimicrobial arena [3,4]. However, in order to be successful, it is crucial to take a proactive, rational approach to determining the pharmacokinetics of a given compound. This starts before the drug is given to humans and continues all the way to regulatory submission.

What is the price to ensure success? It is a commitment to designing every study so the objectives support answering the right questions throughout development, and following up to confirm the study design is executed appropriately. These precautions ensure that the significant costs of incorporating pharmacokinetics into the program are well spent. In this communication, we provide a general framework for incorporating pharmacokinetic evaluations into antimicrobial drug development, provide a brief overview of methodological approaches, and discuss key aspects of clinical study design and execution including common, avoidable pitfalls that can impede successful development.

Planning for success — formulating a pharmacokinetic plan

Conducting pharmacokinetic analyses can be resource intensive and often takes significant time to complete. However, the return on that investment is a more efficient development program in which the potential for success is maximized. But in order to realize that return on investment, it is crucial that pharmacokinetic analyses be treated as an integral part of the drug development plan. Too often, relatively little priority is given to optimizing pharmacokinetic analyses as these data are often considered less crucial than the clinical evaluations that will ultimately be used to gain regulatory approval. However, it is important to foster a system-wide mindset that prioritizes pharmacokinetic analyses as an integral part of a product's development plan as these data will ultimately facilitate regulatory approval. By establishing a pharmacokinetic plan early in development, knowledge gained with each study/analysis will help to inform the design of and need for subsequent studies, thus

Figure 1



Pharmacokinetic pathway to regulatory approval.
[a] In some cases, Phase 2 may be reduced to Phase 1b or 2a studies in which PK data from relevant patient populations are combined with extensive preclinical PK-PD data to support dose selection and hence, initiation of Phase 3 studies.

maximizing efficiencies along the way. An overview of this process is depicted in Figure 1.

The pharmacokinetic plan should start in advance of the drug candidate being administered to humans. Information regarding protein binding, basic pharmacokinetic characteristics (distribution, metabolism and excretion), and the potential for drug–drug interactions should be obtained from *in vitro* and *in vivo* studies as early as possible in the life of the program. The information obtained will determine the overall path forward from a pharmacokinetic standpoint. Early signals regarding the complexity of a compound's pharmacokinetics will help to determine which Phase 1 studies are needed. For instance, data recently published for a novel anti-candidal agent, TSC-INH, indicated that only 5.3% of this compound is excreted in the urine and feces, and is mostly cleared via metabolic pathways [5]. Given the primary elimination pathway and that many drug–drug interactions occur via inhibition or induction of metabolizing enzymes, there is a high probability of drug–drug interactions. Moreover, a significant portion of drug metabolism occurs in the liver and hepatic impairment could significantly alter clearance for drugs eliminated primarily through metabolism. Therefore, a rational decision would be to consider drug–drug interaction and hepatic impairment studies over a renal impairment study given that renal impairment is not likely to greatly effect TSC-INH concentrations in patients.

Early-stage pharmacokinetics can also help to determine the analytical approach required once human data become available. As will be described in greater detail below, data from Phase 1 studies can often be analyzed quickly using non-compartmental methods. However, while non-compartmental models are useful for providing basic pharmacokinetic information on a timely basis (e.g. simple estimates of drug exposures, terminal elimination half-lives, etc.), it is important to allow time for the development of a compartmental pharmacokinetic model